FOOD AND DRUG ADMINISTRATION

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ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

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62ND MEETING

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FRIDAY,

NOVEMBER 21, 1997

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The Committee met at the Holiday Inn, Versailles Room 3 and 4, Bethesda, Maryland, at 8:00 a.m., William Craig, M.D. Chairman, presiding.

COMMITTEE MEMBERS PRESENT:

WILLIAM CRAIG, M.D.	Chairman
ERMONA McGOODWIN, M.D.	Executive Secretary
PARVIN AZIMI, M.D.	
ROBERT L. DANNER, M.D.	
NANCY HENRY, M.D.	
MARIAN MELISH, M.D.	
CARL NORDEN, M.D.	
DONALD PARKER, M.D.	
KEITH A. RODVOLD, Pharm.D.	

GUESTS AND CONSULTANTS:

STACEY C. FITZSIMMONS, Ph.D.
ALICE S. PRINCE, M.D.
BARTH RELLER, M.D.

MEDICAL OFFICERS:

MARIANNE MANN, M.D.
JOHN ALEXANDER, M.D.

ALSO PRESENT:

GARY CHIKAMI, M.D.
JANICE SORETH, M.D.

PRESENTING ON BEHALF OF PATHOGENESIS CORPORATION:

MICHAEL BOWMAN, M.D.
BRUCE MONTGOMERY, M.D.
WILLIAM PITLICK, Ph.D.
JOANNE QUAN, M.D.

A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S

(8:04 a.m.)

CHAIRMAN CRAIG: Good morning. I'd like to welcome you to the third day of the 62nd Anti-Infective Drugs Advisory Committee Meeting.

I think we'll start, first, going around the room and making sure that everybody gets their name on the record. Why don't we start with Dr. Danner.

DR. DANNER: Robert Danner, Critical Care Medicine Department, National Institutes of Health.

DR. AZIMI: Parvin Azimi, Pediatric Infectious Diseases, Children's Hospital, Oakland, California.

CHAIRMAN CRAIG: Bill Craig, University of Wisconsin, Adult Infectious Disease, and Chair of the committee.

DR. McGOODWIN: Ermona McGoodwin, FDA.

DR. HENRY: Nancy Henry, Pediatric Infectious Diseases, Mayo Clinic, Rochester, Minnesota.

DR. RODVOLD: Keith Rodvold, University of Illinois, Colleges of Pharmacy and Medicine.

DR. NORDEN: Carl Norden, Infectious Diseases, Cooper Hospital, University of New Jersey

Medical School.

DR. PARKER: Don Parker, Professor, Department of Biostatistics and Epidemiology, University of Oklahoma.

DR. MELISH: Marian Melish, Pediatric Infectious Disease, University of Hawaii School of Medicine.

DR. RELLER: Barth Reller, Infectious Diseases and Clinical Microbiology, Duke University.

DR. ALEXANDER: John Alexander, Medical Officer, FDA.

DR. CHIKAMI: I'm Gary Chikami. I'm the Acting Division Director for Anti-Infectives.

DR. SORETH: I'm Janice Soreth, the Medical Team Leader in Anti-Infectives.

CHAIRMAN CRAIG: Ermona, do you want to read the conflict of interest statement?

DR. McGOODWIN: Thanks, Dr. Craig.

The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency is determined that all reported interests in firms

regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting.

With respect to FDA's invited guests, there are reported interests that we believe should be made public to allow the participants to objectively evaluate their comments.

Stacey FitzSimmons, Dr. FitzSimmons, Director of Clinical Research at the Cystic Fibrosis Foundation, would like to disclose for the record that the Cystic Fibrosis Foundation has signed a royalty-sharing payback agreement with PathoGenesis Corporation on January 1, '94, to cover the costs expended by Cystic Fibrosis Foundation for their investment in Phase I and II tobramycin studies.

Further, Dr. FitzSimmons also reports that she owns a minimal amount of stock in PathoGenesis. Lastly, Dr. FitzSimmons reports that over the last few years she has served as an unpaid consultant to PathoGenesis. She provided scientific input into their cystic fibrosis research.

In the event that the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a financial interest, the participants are aware of the need to exclude

themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firms whose products they may wish to comment upon.

Thank you.

CHAIRMAN CRAIG: Thank you, Ermona.

Next, Gary Chikami will give an introduction for the FDA.

DR. CHIKAMI: Thank you, Dr. Craig.

Good morning. I'd like to welcome our committee members back to today's session. I'd like to also welcome our guests, and also PathoGenesis Corporation, who is the pharmaceutical sponsor for today's discussion.

The topic for today is a new NDA application for a tobramycin solution for inhalation for the management of cystic fibrosis patients. This application represents several novel issues for this committee. While the drug product itself -- tobramycin -- is not new, the proposed route of administration -- that is, by inhalation -- is novel for this committee.

And, secondly, the indication being sought

-- that is, management of cystic fibrosis patients -- the clinical trial designs that were used and the end points -- clinical end points used to demonstrate clinical efficacy are also unique for an anti-infective agent that has come before this committee.

So I think we look forward to the presentations, both by the pharmaceutical sponsors and the FDA reviewers, and the discussion by the committee.

Thanks very much.

CHAIRMAN CRAIG: Thank you, Gary.

Next, Stacey FitzSimmons from the Cystic Fibrosis Foundation will present the cystic fibrosis registry data.

DR. FITZSIMMONS: Good morning, everyone.

I have been asked, as just stated, to discuss the national cystic fibrosis patient registry data describing Pseudomonas aeruginosa in CF patients. And what I'm going to talk about are the age-specific prevalence of Pseudomonas aeruginosa, trends over time, and incidence rates, and then to describe the relationship of Pseudomonas to mortality in CF patients, to lung function, and to hospitalization rates and acute exacerbation rates.

For those of you not familiar with the

Cystic Fibrosis Foundation, it was founded to find a cure and to control cystic fibrosis over 40 years ago. And over 30 years ago, the Foundation initiated its CF care center network, beginning with 32 care centers established in the early '60s, which were following, at that time, almost 3,000 patients, to today we now have a national network of 113 care centers following 21,000 patients.

These specialized care centers deliver comprehensive CF care and specialized diagnosis, imparting the latest treatment advances and serve as a very vital network to facilitate clinical trials. At annual site visits, careful attention is paid to microbiology lab standards pertinent for today's discussion, and to pulmonary function, and sweat tests laboratory standards as well, to ensure high quality care.

In 1966, the Foundation established the national patient registry, initiated with 7,000 patients. Each of our CF care centers is required to submit annual data for every patient seen in a clinic. The CF Foundation has supervised the collection and analysis of these data for over 30 years.

Initially, the registry was utilized for survival curves, for the production of life tables, as

we began with just demographic and mortality and height and weight data. Then, 10 years ago, we added pulmonary function data and respiratory culture data to the registry. And then, after 1989, after the identification of the gene, we added genotype data, which is facilitating interesting phenotype/genotype research. And we now have genotypes on over 50 percent of our patients.

We continue to add more data over time and have been able to add the collection of up to four measures of pulmonary function values and height and weight data to evaluate a number of new therapies, where we have wanted to be able to address the efficacy and the safety of new interventions that have been added over time.

This site shows the age distribution of our CF patients. They range in age from newborn to 72 years is the age of our oldest patient. And one of the points I wanted to make on this slide is that cystic fibrosis is no longer a pediatric disease. Thirty-six percent of our patients are adults. The mean age is 16. The median age is 14.

The median survival has seen remarkable advances, and particularly between 1980 and 1990 we saw an advance from 18 to 29 years of age. These

improvements have been attributed generally to three things. The first is the receiving of specialized care at our CF care center network. The second is much more aggressive nutritional intervention. And the third has been the availability of new antibiotics in the 1980s -- the quinolones, the monobactams, and the carbopenams.

And with the availability of these new antibiotics that have increased activity against Pseudomonas aeruginosa, we now often deliver these antibiotics in combination and using novel delivery systems. And we believe all of these factors have contributed to the increase in survival.

However, since 1990, there has been -- these gains have not been as dramatic, and they're not sufficient. We have a need to continue to identify effective new treatment strategies.

We have long observed a pronounced survival advantage for our CF males. And although it may be diminishing in recent years -- it started out with six -- five years and has varied somewhat -- the interesting thing that I'll describe in a few minutes is there are very clear differences in the impact of Pseudomonas aeruginosa on females.

Let me say a quick thing about pulmonary

function tests. Pulmonary function tests are a very sensitive tool to characterize and follow the condition of someone's lung function and enable us to depict subtle, and even not-so-subtle, changes in lung function. FEV1 and FVC are widely used to evaluate lung function and to determine the degree of bronchial obstruction.

FEV1 signifies the forced expiratory volume in one second, and it's the amount of air that can be forcibly expired during one second. And it's a very good indicator of blockage, particularly in the large central bronchi.

The more obstruction there is in the lungs, the more difficult it is to get air out quickly; and, hence, the lower, the smaller, the FEV1. FVC stands for the forced vital capacity, which is the maximum amount of air expired after a full inspiration.

These data are shown here as Knudsen percent predicted. That's a method of presenting lung function data that standardizes lung volume by age, sex, and height standardized equations. This here on the left shows the distribution of the percent predicted FEV1 in our CF patients age five and older. Why age five? Pulmonary function tests are very

effort-dependent and require physical effort and patient cooperation, and generally patients under age six are unable to complete reliable, reproducible PFTs.

In cystic fibrosis, we generally define pulmonary function status in four groups -- severe, defined as a percent predicted FEV1 less than 40; moderate, 40 to 69 percent; mild, 70 to 89 percent; and normal, greater than 90 percent. And most of the people in this room's FEV1 percent predicted would be over 100 percent. That is not the case in CF.

In the tobramycin clinical trial, the sample included patients between the 25th percentile and the 75th percentile, which includes about 45 percent of our patients.

Bacterial infection plays a very central role in the progression of lung disease in cystic fibrosis, and the respiratory microbiology results are reported for the majority of CF patients each year in our patient registry. Sputum samples are obtained for the majority -- 67 percent -- and for the non-sputum producing patients throat swabs are obtained, and for a very small majority bronchoscopy specimens are obtained.

Clearly, the leading pathogen of

Pseudomonas aeruginosa was 60 percent of our patients cultured positive. But the results that are shown here show that CF patients culture positive with a number of other bacterial species and fungus aspergillus.

And some of these other gram-negative pathogens will be important to us in the registry and for the effort discussed today, to be able to follow to see if there are emergence of any other pathogens intrinsically resistant to tobramycin, such as Burkholderia cepacia, Stenotrophomonas maltophilia, and Alcaligenes.

We have only recently begun collection of resistance data, methosone resistant staph aureus, and we have plans to assess Pseudomonas aeruginosa resistant to TOBI and to other agents.

What I want to talk about next, briefly, age-specific prevalence trends of Pseudomonas aeruginosa, trends over time, and incidence rates. This slide shows the age-specific prevalence of pathogens that our patients are colonized with. Generally, staff aureus and haemophilus influenza occur early in childhood.

But lung infections with Pseudomonas aeruginosa, shown in the yellow line, occur and become

the predominant pathogen as early as age six. By adulthood, over 80 percent of our patients are colonized with Pseudomonas aeruginosa.

Between ages six to about 15, you can see in this slide, in the blue line, that cystic fibrosis girls seem to become first colonized at higher rates than males. In light of the poorer survival of females, there may be a clue here that early aggressive intervention may have a significant impact.

The prevalence of Pseudomonas aeruginosa has changed very little over the last five years. In this analysis, we are able to calculate the number of new cases of Pseudomonas aeruginosa. In a sample of 3,698 patients followed over three years, who had two negative cultures for Pseudomonas aeruginosa, 20.5 percent -- or 757 patients -- converted to Pseudomonas aeruginosa. And that is -- we've repeated this analysis through the years. That is characteristic of the conversion rate -- very high infection rate every year, 20 percent new cases.

What is the relationship between Pseudomonas aeruginosa and mortality and median survival age? First, in this slide, we've presented death rates by colonization status and by age group. And, first, look at the bottom one. N. flora is not

a new microorganism. It's a mistake. It should be normal flora, not N. flora.

(Laughter.)

So if you compare Pseudomonas aeruginosa to normal flora, the first striking thing you can see is that those patients colonized with Pseudomonas aeruginosa have eightfold greater death rate. And this is true for those under age 18.1 compared to .8, .2 compared to 1.5. And for adults, the increased death rate is over twofold greater.

This slide presents median survival estimates generated from life tables using our registry data from 1991 to 1995. And during this period, the overall survival was 30. For those colonized with Pseudomonas aeruginosa, the overall survival was 29. For the patients who never were colonized with Pseudomonas, there is a statistically increased median survival of 36.

And what is particularly impressive here is if our patients are never colonized with either Pseudomonas aeruginosa or Burkholderia cepacia, their median survival is 51.

In a paper published this year in The Journal of Epidemiology by Dr. Margaret Rosenfeld from the University of Washington-Seattle, we calculated

the relative risk of death in cystic fibrosis children seen at our CF care centers.

And the striking feature of this multi-variate analysis is that even when you control for multiple variables, including severity of lung function -- and here you can see the risk of death for those in the moderate pulmonary function category are 11 times greater; those in the severe, 27-1/2 times greater.

Even in this constellation of factors, Pseudomonas aeruginosa is an independent risk factor for death and explains people colonized with Pseudomonas aeruginosa experience almost twice the death rates.

In this next slide, with the next section I want to talk briefly about the relationship of Pseudomonas aeruginosa to pulmonary function level and to the rates of FEV1 decline annually.

This slide shows the age adjusted mean percent predicted FEV1 by colonization status. People with normal flora have an average 87.7 percent predicted FEV1. For those with Pseudomonas aeruginosa -- let's see, that's actually -- I put up the wrong slide. Let's see if it's next. No, it's not.

Those with Pseudomonas aeruginosa in age

adjusted analyses have a considerably lower mean percent predicted FEV1 of 64.5 percent.

The prevalence of Pseudomonas aeruginosa infection is shown here by age group. The three age groups are children, age zero to 10; teenagers, 11 to 20; and adults, 21 and older. And we've classified the patients by pulmonary -- by the four groups of pulmonary function level, and you can see here that for Pseudomonas aeruginosa there is a striking gradient, with the highest rate of Pseudomonas infection among those with the worst pulmonary function across all three age groups.

The next few slides represent some work in progress with two colleagues, Dr. Lloyd Edwards at the University of North Carolina, and Dr. Mike Konstan in Cleveland at Rainbow Baby and Children's. In these analyses, we use the SAS mixed model, or the random effects regression model, to adjust for the multiple correlations and biases created by repeat measures in serial measures of FEV1 collected in almost 19,000 patients that were followed for over six years, and we have over 150,000 measures of pulmonary function in this analysis.

Cystic fibrosis is characterized by progressive pulmonary disease, and this shows for our

patients from age six and older the annual pulmonary function decline is 1.9 percent predicted FEV1 per year in children, and is half that -- 1.1 -- in adults each year.

Gender differences are observed for female children in these annual rates of decline. They are significantly greater -- 2.1 for females, 15 percent greater than males. There are no statistically significant differences in adults.

For Pseudomonas aeruginosa colonization, these patients experience a significantly greater rate of decline -- 1.9 percent predicted FEV1 per year for children, a 36 percent greater decline each year than for those not colonized with Pseudomonas aeruginosa, with no differences in adults.

However, when these analyses are stratified by sex, the females infected or colonized positive with Pseudomonas aeruginosa decline 15 percent more per year than the males colonized with Pseudomonas aeruginosa. And even among the adults colonized, there is a statistically significant difference in the decline of the female adults -- a 20 percent greater decline.

This slide shows the annual decline stratified by the four levels of pulmonary function --

normal, mild, moderate, severe -- by age group -- the children and the adults. And the point here is that children colonized with Pseudomonas aeruginosa -- shown in the red -- decline faster, in the 1.8 compared to 1.3; decline almost three times faster in the mild group, .9 compared to .2, .7 compared to a slight increase even in those non-colonized.

And even more alarming or more significant, in adults that presumably had never been colonized until later in life, who start out with very normal function, when they're first hit with Pseudomonas aeruginosa, their decline is six, seven times faster than adults not colonized with Pseudomonas aeruginosa.

So in the last slide I want to show the relationship between Pseudomonas aeruginosa and hospitalization rates and acute exacerbation rates. If you look at the bottom row, labeled "All" -- but first we can summarize. In the patients colonized with Pseudomonas aeruginosa, they experience more than twice the percent hospitalized more than one time a year -- 52 percent compared to 20 percent a year.

The mean hospitalization rate of those colonized with Pseudomonas aeruginosa is three times higher than those not colonized with Pseudomonas

aeruginosa -- 1.1 versus 0.4. The length of stay is longer, 10 days versus 8.7, in those colonized with Pseudomonas aeruginosa experiencing a hospitalization.

And mean acute exacerbation -- that's defined as IV antibiotic use in either a hospital setting or received at home -- the rates, again, are almost four times higher in those patients colonized with Pseudomonas aeruginosa. And if you look at the patients in the two lowest pulmonary function groups, roughly the patients eligible for the tobramycin study, the same relationships hold up.

So, in summary, I just want to say that we have strong evidence from the CF Foundation patient registry that Pseudomonas aeruginosa severely affects the health of individuals with cystic fibrosis. Compared to those patients not colonized with Pseudomonas, those colonized have poor pulmonary function, their pulmonary function declines much faster, they are hospitalized twice as often, they stay in the hospital longer for each stay, and they have up to eight times higher mortality rates. Clearly, more effective treatment of Pseudomonas would be of great benefit for CF patients.

Thank you.

CHAIRMAN CRAIG: Thank you.

Questions for Dr. FitzSimmons?

Okay. And also, for the record, thank you, Dr. FitzSimmons, very much for that introduction.

And also, for the record, I'd like to acknowledge that Alice Prince from Pediatric Infectious Disease at Columbia University has joined the committee.

The next presentation is the sponsor presentation by PathoGenesis Corporation.

DR. PITLICK: Good morning. I'm Bill Pitlick, Director of Regulatory Affairs for PathoGenesis Corporation.

On behalf of PathoGenesis, I'd like to thank the agency, first of all, for giving us this opportunity today to share with this committee some very exciting data on tobramycin solutions for inhalation, or TOBI, in the treatment of people with CF lung disease.

Before we begin, I'd like to acknowledge the effort and dedication of the division in expediting the review of our application, and I'd also like to acknowledge the agency itself for the tremendous cooperation we have received throughout the development of TOBI.

But most of all, I'd like to acknowledge

the efforts of the CF community, the people with CF, their caregivers, the physicians, the families, and particularly the CF Foundation, for without their tremendous cooperation, participation, and support, we would not be here today.

I'd also like to say good morning to the people in Seattle who came to the office this morning at 5:00 to watch this on TV.

(Laughter.)

Before we begin, let me describe the agenda for our presentation this morning. Dr. Bonnie Ramsey of Children's Hospital in Seattle, the principal investigator on our Phase III trials, is going to give the committee some additional background on CF disease and outcome measures. I'll give a brief overview of the development of TOBI.

Dr. Bruce Montgomery, our Senior Vice President for Research and Development, will present the critical trial results of microbiology and clinical efficacy. Dr. Joanne Quan, the Director of Medical Affairs of PathoGenesis, will present the clinical safety data from our Phase III trials. And, finally, Dr. Michael Bowman of Children's Hospital of Los Angeles will present a risk-benefit analysis from the perspective of a clinical caregiver.

Before we begin, I'd ask that you hold your questions until after we have completed our presentation, and our presentation will last approximately 90 minutes.

It now gives me great pleasure to introduce Dr. Bonnie Ramsey, one of the world's leading experts on CF research and patient care.

Dr. Ramsey?

DR. RAMSEY: Good morning.

Cystic fibrosis is the most common fatal genetic disorder in the caucasian population, with a carrier rate of approximately five percent and an annual incidence of one in 2,000 live births. This autosomal recessive disorder is caused by mutations in a single gene on chromosome 7, which encodes for the cystic fibrosis transmembrane regulator protein, or CFTR.

This protein, located on the apical membrane of epithelial cells, is the cyclic ANP regulated ion channel. And abnormalities in this protein lead to decreased chloride secretion and increased sodium absorption in these cells.

The common pathologic finding in affected organs is inspissated mucus secretions which block expectory ducts, and they lead to fibrosis and organ

dysfunction. This results in the clinical manifestations which include recurrent upper and lower respiratory tract infections by pathogens such as Pseudomonas aeruginosa, which was just previously described to you, pancreatic insufficiency with malabsorption, biliary cirrhosis, and male infertility.

The illness today remains fatal. Over 90 percent of the deaths are attributed to lung failure and its associated complications. Thus, new treatments directed primarily at slowing the progression of disease are of utmost importance.

What I am going to show you in the next few slides is a review of the progressive pathologic changes in the lung disease of cystic fibrosis.

This slide shows the earliest changes in the lung of patients with cystic fibrosis. This was taken from a two-year old who died of sudden infant death syndrome who had very mild involvement. And what you first see is hypertrophy of the submucosal glands. However, the remaining part of the epithelium is relatively normal, which is traditional for CF.

Next slide?

This second slide shows the classic changes of cystic fibrosis, where you have sparing of

the lung karyenchyma and alveolar spaces, and marked endobronchial and peribronchular inflammation. The airways are absolutely full of mucus, cellular debris, and bacterial pathogens.

However, there are almost no intracellular or peritoneal bacteria. It's very common for this entire area to be entirely sterile. Therefore, it is absolutely critical that the highest concentrations of antibiotic be in this peribronchular/endobrochular space.

Next, please?

Now, this higher power micrograph shows you that you have a very predominant neutrophilic influx. It's very pathomnemonic of this illness, whereas the epithelium remains intact. You also get the neutrophil influx into the submucosal space.

However, where you're going to see bacteria is out here. They will not be intracellular, and they are not in the submucosal area.

Next slide?

This final slide shows the destruction of lung tissue, which is the end stage of cystic fibrosis. You have what is classic bronchiectasis. Because of all of the proteolytic enzymes, you have destruction of support tissue. In association, you

get complications such as mucus plugging and areas of hemoptysis.

Next slide?

And so how do we intervene with this relentless progressive pathology? Well, the hallmark of care of patients with cystic fibrosis, which is followed in all of the 113 centers that Stacey described, is a combination of routine quarterly monitoring of health status, primarily directed to nutrition and lung disease.

For the pancreatic disease, there is replacement with enzymes and vitamin supplements, as well as nutritional supplements. For pulmonary disease, there is emphasis on airway clearance techniques, appropriate antibiotic therapy, and other adjunctive therapies such as bronchodilators, anti-inflammatory therapies, and Pulmozyme.

There is also a constant surveillance for other manifestations of the illness, commonly liver disease, diabetes, and sinus disease, which can occur in many of the patients, particularly some of the older patients.

Next slide?

In spite of our very diligent observation of these patients, they continue to have exacerbations

in their illness. Now, this is an actual reproduction of pulmonary functions from a nine-year old patient followed in my center in Seattle, Washington. She has moderate lung disease. She would have been a candidate for the tobramycin study. However, she was not in the study, so this is showing routine care.

During a one-year period in 1996, she had, as you can see, one, two, three, four episodes where she had a decline in pulmonary function associated with increased cough, increased sputum production, and general fatigue. This is what we term a pulmonary exacerbation.

On three occasions -- one, two, three -- you can see that we hospitalized her to receive IV anti-pseudomonal therapy. At each point, she had an improvement in lung function. Here she was treated with oral antibiotics. And although there was a transient improvement, if you look over the entire year she had exactly a two percent dropoff in lung function, which is consistent with what Stacey reported to you for a girl this age.

Next slide?

How do we treat pulmonary exacerbations? Usually, it is a combination of intravenous anti-pseudomonal antibiotics, a combination of

aminoglycoside and betalactam. In addition, we have aggressive pulmonary toilet with other supportive measures, as I defined previously to you. The duration will usually range from 14 to 21 days. It often starts in the hospital, but now, in the 1990s, patients are usually sent home as well on IV antibiotics.

Clinical response -- physicians will follow physical examination, including respiratory rate, chest exam. Pulmonary functions are a very key outcome, which are used to decide the end of therapy. Physicians will look for an improvement in FEV1 of roughly 10 to 20 percent, 20 percent being the absolute maximum that one sees.

What is not followed is chest X-ray, because this is not usually an acute marker of change in pulmonary function, unless the patient has complications and there is not an expectation of eradication of the bacteria, such as Pseudomonas. Unfortunately, that does not occur.

It was shown by Dr. Regelmann's group at the University of Minnesota that you will usually get roughly a one- to two-log drop in bacterial density during a cleanout, which is what we call them. We also looked for improvements in general health. I can

assure you that a patient can feel a change of 10 to 15 percent in lung function.

Next slide?

Until the last decade, all treatments were directed towards -- all IV antibiotic treatment was directed towards acute pulmonary exacerbations, but there was very little impact on either the progressive decline in pulmonary function, which I showed you -- the two percent per year -- or the frequency of these exacerbations.

However, the CF community has begun looking at potential chronic therapies, of which Pulmozyme was the first example. But there was significant reservation initially among clinical scientists at such trials, because of the feasibility of being able to see efficacy in this patient population, and the reasons are shown here.

Because of the progressive nature of the illness, there have been strong period effects over time with the ongoing decline. There is a wide variation in illness severity, as you've just seen. And there is also this occurrence of periodic exacerbations. If you combine all of these factors, you have a very large intra and intrasubject variability in the commonly used outcomes, such as

lung functions or even bacterial density. In addition, you have confounding effects of multi-organ dysfunction impacting on the pulmonary disease.

Well, in order to meet these challenges, the CF Foundation convened a consensus meeting, with participation from the FDA, initially in December 1992. I was fortunate to be able to chair that consensus conference with Dr. Tom Boat from the University of Cincinnati, and you have a copy of the summary of that meeting in your book.

A summary -- what we determined at that time were several recommendations and then a list of future goals. In terms of study design, the key recommendations were the following. There was clearly a need for large, randomized, placebo-controlled, multi-center trials. Now, that may seem odd, but up until this time most of the studies were single center.

There was a call for standardization of primary outcome measures and a move from cross-sectional to longitudinal studies, as well as development of appropriate analytic tools.

Over the next four years, significant progress in clinical trials was evidenced by the publication of three large trials in the CF population

which were published in The New England Journal of Medicine -- aerosol tobra, Pulmozyme, which was clearly the largest, and Ibuprofen.

In addition, gene therapy began moving from the laboratory sphere into Phase I trials. Thus, the FDA came back to the CF Foundation and requested a second meeting to relook at clinical outcomes, with particular emphasis at that time on gene therapy. The second meeting was held in the spring of this year here in Washington.

In preparation for the second consensus meeting, the FDA representatives provided all of the participants with a series of questions to help evaluate the validity of each clinical end point. The five questions are listed here, and I will come back to them.

The clinical end points discussed at the conference are summarized in this slide. Pulmonary function will be discussed in the subsequent slides, as FEV1 was felt to be the best to fulfill the criteria outlined in the previous questions.

Microbiology was -- many of the issues were already addressed by Stacey FitzSimmons in her previous presentation. But I do think it's very important to note one of the issues that was raised is

that expectorated sputum was felt to be an accurate measure of lower airway microbiology, as there have been several published reports that have documented high correlation between expectorated sputum and transtracheal aspirates, bronchioavular lavage, and cultured lung tissue.

Both microbiology and markers of inflammatory response were felt, at this time, to be useful clinical outcomes when used in conjunction with another measure, such as pulmonary function, but at this time could not stand alone. Pulmonary exacerbation still does not have a standardized definition, but hospitalization rate and IV antibiotic usage, which Stacey showed you, can be currently acceptable surrogate measures. Imaging techniques have not yet been fully developed, and may be useful in the future.

Now I'm going to go back and review the five questions in relationship to FEV1. Does the marker correlate with the pathophysiology of disease? Yes, FEV1 and other PFT measures correlate with disease severity, and Stacey showed you that.

Does the marker correlate with the clinically meaningful end point? Yes, FEV1 predicts morbidity in terms of health care utilization and IV

antibiotic usage and does predict mortality.

Is the marker specific for the disease process? FEV1, as most of you may know, is used in other lung diseases, very commonly used in asthma studies, but there are factors specific to CF. I think one thing that Stacey clearly showed is that patients have a baseline FEV1 that puts them in a category of mild, moderate, or severe.

With asthma, you frequently expect that between exacerbations they will return to normal. That is not the case here. This is fixed obstructive disease, at least as of 1997. Also, nutritional status, such as weight for age, will impact on FEV1, and, as you saw, microbiologic status.

Is it a reliable measure? This is clearly the biggest advantage of FEV1 currently, or other pulmonary functions -- is that there are standardized equipment and techniques in every center in the country, and there is also normative equations available based on age, height, and gender, not only in the normal population but in the CF population as well.

And, is the predictor used safely? Yes, FEV1 can be used. Obviously, a sudden decline in FEV1 can be representative of bronchospasm or other safety

issues.

Stacey kindly provided me with this slide, which is a summary of clinical trials in the last decade that have used pulmonary function as their primary outcome. As you can see, it is a wide variety of agents showing its clear prevalence for usage.

However, certainly, FEV1 and other pulmonary functions have their limitations, and these include -- there is still this large inter and intrasubject variability. It is effort dependent, so that it is very difficult for children less than five to do it. We are now developing infant pulmonary function testing, but it really is not at a completed state yet. It is affected by intercurrent illnesses.

Now, all of these limitations can be overcome by choosing the appropriate study population and design and having an adequate sample size. In future studies, as we improve our therapies, there is less decline over time. And in future decades, that may become an issue. It means that the sample size keeps getting larger and larger.

So, in conclusion, cystic fibrosis remains a fatal genetic disorder for which new therapies are critically needed to improve survival and decrease morbidity. Design of optimal trials is challenging.

However, the CF community has met this challenge and has successfully completed trials utilizing the following basic principles -- studies are of adequate power and duration to overcome the inherent variability of the clinical end points, efficacy is based on multiple rather than single clinically relevant end points, and PFTs remain the most well-recognized in standardized clinical outcome.

Thank you very much.

DR. PITLICK: Thank you, Dr. Ramsey.

As Dr. Chikami pointed out, tobramycin is an old drug. It was first approved in 1975 for parenteral use in the treatment of gram-negative infections, including those caused by Pseudomonas aeruginosa. And as Drs. Ramsey and FitzSimmons have pointed out this morning, P. aeruginosa is associated with significant morbidity and mortality in people with CF. And for this reason, parenteral use of tobramycin is quite common in treating the exacerbations of chronic lung disease in people with CF.

There are two major problems in using parenteral tobramycin to treat endobronchial infections. First, the concentrations in the sputum after using parenteral administration of labeled doses

often do not exceed the MIC of the infecting organism. And for that reason, larger than recommended doses are often given to achieve efficacious sputum concentration, and herein lies the second problem. These larger doses have a significant potential for systemic toxicity, especially the ototoxicity and nephrotoxicity which are known to occur with aminoglycosides.

Now, a solution to these problems is to deliver tobramycin by inhalation. This approach is very appealing because it maximizes the concentrations of tobramycin at the site of infection -- that is, the endobronchial space. But because absorption is minimal, the risks of systemic toxicity are quite low.

Now, people with CF are now aerosolizing tobramycin with extemporaneously prepared formulations using parenteral products. These formulations are not approved for this indication, and the parenteral products contain preservatives, such as phenol and sodium bisulfite, which present additional risks to these patients. Furthermore, these preparations have not been tested for safety or efficacy.

Therefore, we believe that there is clearly a need for a tobramycin solution for inhalation that is specifically designed and approved

for use in people with CF that is safe and efficacious, preservative-free, and easy to use. Furthermore, we believe that such a product will be of enormous benefit in the chronic treatment of CF lung disease.

Now, many people in the CF community have also recognized the need for an aerosolized antibiotic. In particular, Dr. Arnold Smith, who is here today, has conducted nearly 15 years of in vitro and clinical research on aerosolized antibiotics, including tobramycin. That research culminated in a randomized, double-blind, clinical trial in 71 people with CF, conducted by Drs. Smith and Ramsey and published in The New England Journal of Medicine. And this trial was supported by the CF Foundation.

That study, published in The New England Journal of Medicine in 1993, as Dr. Ramsey noted, demonstrated unequivocally the efficacy of aerosolized tobramycin. And after the results of that study were published, the CF Foundation approached PathoGenesis and asked us to carry on this research with the idea of bringing to the market a tobramycin for inhalation specifically designed for people with CF. And, thus, the development of TOBI has been a cooperative effort between the CF Foundation, PathoGenesis Corporation,

and Children's Hospital of Seattle.

In 1994, the FDA designated tobramycin for inhalation as an orphan product, and on July 10th of this year PathoGenesis filed the NDA for TOBI.

To gain approval for TOBI, we had to accomplish several things, none of which are trivial. First, we had to develop and test a formulation that was stable, preservative-free, and one which could be aerosolized. Next, we had to establish the toxicological profile of an inhaled tobramycin for TOBI. And, finally, we had to demonstrate the clinical safety and efficacy of TOBI in people with CF.

The formulation we developed for TOBI is five milligrams of a 60-milligram solution in quarter normal saline at pH 6.0. The concentration of pH and the osmolality of the solution are all specifically designed to optimize its aerosolization characteristics. TOBI is preservative-free, it's sterile, and non-pyrogenic, to reduce the risk of infection or further insult to the airways.

Finally, TOBI is stable when it's stored under refrigeration, and it is packaged in single dose, easy-to-use, low density polyethylene ampules each containing a single dose of 300 milligrams of

TOBI.

Now, the systemic toxicity of tobramycin, as Dr. Chikami noted, is well known, but we had to evaluate the direct effects of tobramycin on the respiratory tract. To do that, we conducted a chronic study in animals which were exposed every day for six months for up to three hours a day. The doses used in that study resulted in four to 21 times the peak systemic serum levels we subsequently observed in our Phase III trials.

In the six-month study, we found mild to moderate inflammation of the larynx and lungs in both control as well as treated animals, at doses which resulted in ten times the peak serum concentrations which we observed subsequently in Phase III. These respiratory lesions were probably due to chronic inhalation rather than tobramycin itself, and then resolved during the 28-day recovery period at the end of the study. And as you will see in Dr. Montgomery's talk, this finding was very important in the design of our Phase III dosage regimen.

The clinical development program in our NDA consists of one clinical pharmacology study, which we used to determine the appropriate dose/nebulizer combination, and two Phase III randomized, double-

blind clinical trials.

For additional safety data, we included data from a follow-on study and the audiology data from the Ramsey trial.

In this morning's presentation, we will focus on the results of the two Phase III trials.

The clinical data collected provide the basis for an indication for chronic, intermittent, administration of 300 milligrams of TOBI twice daily in conjunction with standard therapies for the treatment of CF patients infected with P. aeruginosa. The data we present today will show that TOBI dramatically improves lung function, reduces sputum bacterial density, reduces the need for hospitalization and the need for additional anti-pseudomonal antibiotic therapies.

Dr. Bruce Montgomery will now present the results of our Phase III clinical trials.

Thank you.

DR. MONTGOMERY: Good morning.

This morning I will present the design of the Phase III trials conducted by PathoGenesis and the efficacy and microbiology results from these trials. My introduction to the trial design will include a brief description of the aerosol delivery system that

we selected and the rationale for the dose and dosing regimen.

I would like to acknowledge beforehand this dosing regimen owes a great deal to the pioneering work of Drs. Smith and Ramsey on the treatment of cystic fibrosis with aerosolized tobramycin.

PathoGenesis has sponsored two randomized, placebo-controlled studies. These studies were called 002 and 003, and employed an intermittent dosing regimen. The studies consisted of three cycles, each cycle comprised of a 28-day period on drug followed by a 28-day period off drug. Patients were dosed twice a day with either placebo or 300 milligrams tobramycin using a Pari LC PLUS jet nebulizer. During the study, patients received standard therapies for cystic fibrosis in addition to the study drug. Thus, these studies are a comparison of standard care versus standard care plus TOBI.

Unlike other routes of administration, it is difficult to consistently deliver a high dose by inhalation. Nebulizers, which convert drug solutions to a fine mist adequate for breathing, are inefficient. The typical nebulizer delivers approximately 10 percent of the dose placed in the

nebulizer. The rest of the dose is either exhaled, coughed up, or remains behind. Anatomical factors and differences in breathing patterns also contribute to this low level of deposition.

The particle size generated by the nebulizer is also critical in achieving optimal drug deposition. A particle size of three microns is optimal for deposition in the peripheral airways, the site of the infection.

Finally, nebulizers have variable rates of delivery, which can affect compliance. The nebulizer system employed by Dr. Ramsey in her New England Journal study required almost one hour to set up and deliver a single 600-milligram dose, and this was repeated three times a day.

In order to meet these challenges, we have used the best available delivery system -- the Pari LC PLUS nebulizer, in combination with a Pulmo-Aide compressor. This breath-enhanced nebulizer was selected because it improves delivery almost twofold over previous models of jet nebulizers, and because it nebulizes drug quickly -- an important feature for patients. The Pari LC PLUS delivers approximately 15 to 20 percent of the dose in the nebulizer to the lung.

As noted before, the median particle size delivered by the Pari LC PLUS is three microns -- the optimal size for deposition in the peripheral airways at the site of the infection.

We consider four factors in selecting the 300 milligram b.i.d. dose. These included the concentration required to exceed the MIC 90 of P. aeruginosa isolates from CF patient, the concentration required to overcome the inhibitory components in sputum, the results of previous clinical studies, and specific patient compliance issues. These factors will be addressed in the next four slides.

First, the tobramycin MIC 90 of P. aeruginosa isolates in the CF population is higher than in the general hospital population. This may be due to the frequent use of parenteral aminoglycosides in treatment of CF patients. Previous studies have demonstrated that the MIC 90 for CF isolates ranges from eight to 16 micrograms per ml. We use these MIC 90 values as a starting point in our selection of dose.

Next, Dr. Smith and colleagues have conducted in vitro studies documenting the interdiction of tobramycin by sputum. The growth

curves in these studies suggest that in the presence of sputum the concentrations of tobramycin must exceed the MIC by at least 10 times in order to overcome the inhibitory components in sputum and suppress growth of P. aeruginosa.

If a level 25 times the MIC in sputum could be achieved, a larger antimicrobial affect may occur. Thus, a nebulized dose leading to the deposition of a minimum sputum concentration of 10 times the MIC 90 was proposed.

In order to select an appropriate dose for the Phase III studies, we first evaluated the results obtained in other clinical studies of aerosolized tobramycin. These studies used doses ranging from 160 to 2,000 milligrams daily, and indicated that improvements in lung function are dose dependent and greatest at the higher doses. The result suggests that daily doses greater than 240 milligrams would be required to achieve maximum efficacy.

The higher doses were tested to prove the concept that aerosolized tobramycin was efficacious. However, these doses are not practical for long-term use. Therefore, we chose to determine whether adequate sputum concentrations, defined as tenfold the MIC 90 of CF clinical isolates, could be achieved with

a lower dose.

We conducted a Phase II study to measure sputum concentrations following aerosol delivery of the 300-milligram dose. Our target concentration of greater than or equal to 128 micrograms of tobramycin per gram of sputum, approximately 10 times the MIC 90 of P. aeruginosa CF isolates, was achieved in 87 percent of the patients tested. For this reason, we did not test a higher dose before proceeding with Phase III studies.

A modified Pari LC nebulizer became available after the Phase II study, the Pari LC PLUS. In fact, this nebulizer was used in our Phase III studies and improved delivery of tobramycin in the lungs, achieving the threshold level of greater than or equal to 128 micrograms per gram in 96.5 percent of patients. At this concentration, 97.5 percent of patients received 10 times the MIC of their most resistant isolate, and 95 percent of patients received 25 times their highest MIC.

The mean sputum tobramycin sputum concentrations was 1,200 micrograms per gram of sputum. In addition, prior to the Phase III studies, we also had to address the dosing regimen.

The selection of an intermittent 28-day

on/28-day off regimen was made for three reasons. First, and most importantly, the Ramsey study showed that some treatment effect was maintained for 28 days after therapy was discontinued.

Second, the histological changes observed in the animal studies resolved within 28 days after therapy was discontinued.

Third, intermittent dosing may decrease the incidence of microbial resistance. Previous studies have demonstrated that P. aeruginosa with higher MICs revert to lower MICs when antibiotic therapy is discontinued.

The final consideration of selecting an appropriate dosing regimen was compliance. A regimen which is impractical may not be used. Thus, we designed our regimen to increase compliance. First, we chose b.i.d. dosing rather than t.i.d. dosing, to eliminate the need for a midday dose. As already mentioned, nebulization time can be significant and creates difficulties for patients by causing missed time from work or school. We also used a more convenient, low volume, premixed, single-use ampule, so treatment time was approximately 10 to 15 minutes.

Based on these prior considerations, the dosing regimen selecting for the Phase III trials was

an intermittent 28 days on/28 days off aerosol delivery of 300 milligrams b.i.d. This dose was administered via the Pari LC PLUS nebulizer.

The hypothesis we tested in our Phase III trials was at TOBI, administered as chronic, intermittent, suppressive therapy for cystic fibrosis patients infected with P. aeruginosa, will improve lung function, decrease sputum bacterial density, and decrease hospitalization and intravenous anti-pseudomonal antibiotic use.

First, I want to discuss our choice of efficacy end points. As mentioned by both Dr. FitzSimmons and Dr. Ramsey, FEV1 and FVC are the single best predictors of mortality in cystic fibrosis. We chose FEV1 and FVC as the primary clinical efficacy end points.

Since cystic fibrosis is characterized by a progressive loss of lung function -- on average two percent per year -- improvements in FEV1 and FVC are meaningful, both in the near and longer term. Today, I will present the FEV1 data from our two Phase III studies. The FVC changes parallel the FEV1 changes, so I will present only the FEV1 data.

The bacterial density, as measured by colony-forming units -- that is, CFUs -- per gram of

sputum was the antimicrobial efficacy end point. Unlike most antibiotic therapies where eradication or cure is the end point, TOBI is intended as suppressive therapy. CFUs per gram of sputum has been used in prior short-term CF studies but has not been shown to correlate well with clinical efficacy measures.

Hospitalization and intravenous anti-pseudomonal antibiotic use were among the secondary efficacy end points in the Phase III studies. These are important measures and medical interventions for cystic fibrosis patients. These interventions are expensive, disrupt school, work, and family life. In addition, they have been used in past cystic fibrosis studies as measures of efficacy and quality of life.

I will now review in detail the study design for the two randomized placebo-controlled studies. During a four-week screening period, which is right here, initial sputum cultures were obtained. Throughout the study period, physicians were allowed to treat patients with standard therapies for cystic fibrosis, which might include anti-pseudomonal antibiotics. However, other aerosolizing antibiotics were not allowed.

Therefore, the study is actually a comparison of standard care for cystic fibrosis versus

standard care plus TOBI. The studies consisted of three cycles, each cycle comprised of 28 days on drug, followed by 28 days off drug.

The following inclusion criteria were designed to include a broad segment of the CF population -- patients at least six years of age with documented cystic fibrosis; FEV1 percent predicted based on gender, age, and height, between 25 and 75 percent; P. aeruginosa present in sputum; and room air oximetry bigger than 88 percent. The FEV1 criteria were chosen to include a patient population that was likely to be hospitalized, allowing us to evaluate and effect their hospitalization.

Patients were excluded for recent massive hemoptysis, renal insufficiency, and culture of Burkholderia cepacia from sputum. B. cepacia is intrinsically resistant to tobramycin. It is important to note, also, that patients with P. aeruginosa isolates with high MICs, classified as resistant to parenteral therapy, were not excluded from the study.

All of our analyses presented today are based on an intent to treat population, i.e. all patients who received at least one dose of study drug. The relative improvement over baseline of FEV1 was

analyzed at 20 weeks, which is the end of the third on drug treatment period. Treatment effect is expressed as relative change in TOBI group minus the relative change in placebo.

Please note that all raw FEV1 data is normalized to percent predicted based on age, height, and gender prior to analysis. They use the relative changes because it normalizes for different baseline severity of illness. For instance, a four percent absolute improvement in a patient with a baseline of 40 percent is probably as important as a seven percent in a patient with a baseline of 70 percent. Relative change is also how the results in the DNase trials have been reported.

The absolute change from baseline in bacterial density was analyzed at 20 weeks. The treatment effect is to defined as the absolute change in the TOBI group minus the absolute change in the placebo.

Hospitalization and intravenous antibiotic use were preplanned to be analyzed using data from the two Phase III studies combined. For each of these end points, two analyses were conducted -- the number of days over six months and the relative risk as compared with placebo.

I am now going to present the efficacy results from the two Phase III studies. First, I will present the 002 study, then the 003 study, and then the combined analysis of the 002 and 003 studies.

Twenty-nine cystic fibrosis centers participated in this trial as shown by the red stars on this map. As you can see, the study includes centers which are geographically well distributed across the United States.

There were 223 patients enrolled in the study. Approximately 90 percent of the patients completed the study. Dropout rates were comparable between the two treatment groups. As shown by the small number of withdrawals in each cycle, the regimen was well accepted by patients in this study.

The average age in the study was 20 years. Most patients produced at sputum at screening. The mean FEV1 was close to 50 percent at baseline, and DNase use was very common in both groups. A comparable number of patients in each treatment group entered the study with Pseudomonas isolates with MICs to tobramycin greater than or equal to eight micrograms per ml.

This graph demonstrates dramatic improvement in lung function with TOBI. On the

Y axis, lung function is shown as the mean relative change from baseline in the FEV1 percent predicted. On the X axis, weeks are shown, displaying -- noting each study visit.

Lung function improved dramatically by two weeks in the TOBI group. Lung function was maintained above baseline, even in the off drug study periods. In contrast, the placebo group had little change in lung function over the 24 weeks, while receiving standard CF therapies.

The FEV1 treatment effect at week 20 was 12.5 percent. In fact, this is the largest treatment effect ever seen in a Phase II or Phase III cystic fibrosis trial over a similar time period. Almost all of the treatment effect was due to improved lung function in the TOBI group.

The antimicrobial efficacy analysis showed that the bacterial density in the sputum decreased with each treatment cycle. Weeks are displayed on the X axis. On the Y axis, CFUs per gram of sputum are displayed. As you can see, the density decreases during the on drug period, but quickly approaches baseline values during the off drug period. In addition, by the third treatment cycle, the magnitude of the decreases decline from that seen in the first

two cycles.

Clearly, sputum bacterial density is not closely correlated with FEV1, which was 12 percent above baseline at this point, which is the end of the on drug period in the third treatment cycle.

The treatment effect at 20 weeks, which is the third of the on drug treatment cycle, was a decrease of about one log. The sputum P. aeruginosa density had decreased from baseline in TOBI patients but had increased in placebo patients.

I will now show you the results of the other Phase III studies, 003.

Forty cystic fibrosis centers participated in this trial, as shown by the red stars on this map. As you can see, the study includes centers which are geographically distributed across the United States.

There were 297 patients enrolled in this study. As seen in the 002 study, approximately 90 percent of the patients completed the study. Withdrawals were comparable between the two treatment groups overall and during each cycle.

The patient profile in the study was similar to that in the 002 study. The average age in both groups was 21 years, and the mean FEV1, again, was close to 50 percent at baseline. Again, DNase use

was very common, and the MICs were similar to that seen in the 002 study.

Again, we see the dramatic improvement in lung function on TOBI therapy. Lung function was improved by two weeks and was maintained above baseline, even during the off drug periods, for the six-month trial. The placebo group had a decreased FEV1 over the course of this study.

The FEV1 treatment effect at week 20, which is the end of the third on drug cycle, was 11.4 percent. This was similar to the treatment effect of 12.5 percent observed in the 002 study. Most of the treatment effect was due to improved lung function in the TOBI group.

The antimicrobial efficacy analysis showed a similar pattern to the 002 study. As noted before, we saw a decrease on drug period with a return to baseline during the off drug period. As noted before also, sputum bacterial density is not closely correlated with clinical efficacy, since during the third cycle lung function at this point in time was improved in the TOBI group 8.7 percent above baseline.

The treatment effect, though, at that point -- 20 weeks in the study -- was a decrease of one log, similar to that seen in the 002 study. The

sputum P. aeruginosa density had decreased from baseline in TOBI patients, but, again, had increased in the placebo patients.

I will now present the secondary analyses. These analyses were preplanned using data combined from both studies. The first secondary analysis is the risk of hospitalization. This figure shows that a TOBI patient was 26 percent less likely to be hospitalized, this placebo patient. The Y axis shows the percentage of patients hospitalized, and the X axis shows the number of weeks.

The Kaplan-Meier curves start diverging by four weeks and continue to separate with subsequent cycles of therapy.

The combined analysis of days hospitalized showed a significant difference between treatment groups. The mean number of days hospitalized in the TOBI group was 5.1, as compared to 8.1 in the placebo group. This represents a savings of three days, on average, over a six-month period.

Another secondary analysis is treatment with IV anti-pseudomonal antibiotics. This figure shows that a TOBI patient was 36 percent less likely to be treated with intravenous anti-pseudomonal antibiotics than a placebo patient. As with

hospitalization, the Kaplan-Meier curves start diverging by four weeks and continue to separate with subsequent cycles of therapy.

The combined analysis showed TOBI patients were treated with intravenous anti-pseudomonal antibiotics for significantly fewer days than placebo patients. The mean number of days treated with anti-pseudomonal antibiotics in the TOBI group was 9.6, as compared to 14.1 in the placebo group. This represents a savings of 4.5 days, on average, over a six-month period.

Subgroup analysis of FEV1 percent predicted were performed, grouping patients by age, gender, disease severity, and DNase use. The first column shows the number of patients in each subgroup. The second column -- this first column is the treatment group. The second is the number of patients. The third column is the treatment effect.

As you can see in the third column, within every subgroup the mean relative change in FEV1 at week 20 was greater in TOBI patients than the placebo patients. The fourth column shows the P value, comparing TOBI and placebo. Statistical significance was achieved in all but one smaller group -- the group aged six to 12. However, in this group, the FVC

treatment effect was significant.

This answers the second panel question you have been asked today. TOBI is efficacious in all subgroups.

I will now compare the results of the two Phase III studies. The treatment effect for FEV1 was similar in both studies. However, when comparing to initial baseline, placebo patients in the 002 study had little decline in lung function, while the 003 placebo patients had a 2.7 percent decline.

For CFUs, both studies had nearly identical antibiotic effects, suggesting the differences in these studies were not due to differences in antimicrobial efficacy.

Although hospitalization and intravenous antibiotic use were a preplanned combined analysis, we also analyzed the effects separately in both studies. The risk of first hospitalization in days was significant in the 002 study. The risk for first hospitalization in the 003 study was not significant. The days hospitalized in the 003 study trended towards significance.

For intravenous antibiotic use, the risk and days was significant in both studies. The effect, however, was stronger in the 002 study. Overall, both

studies show consistent effects in almost all end points.

The efficacy conclusions from these studies are definitive. We have demonstrated that TOBI-administered as chronic, intermittent, suppressive therapy for cystic fibrosis patients improves lung function, a treatment effect of 11 to 12 percent, decreases sputum bacterial density, decreases hospitalization -- a 26 percent decreased risk -- and decreases intravenous anti-pseudomonal antibiotic use -- a 36 percent decreased risk. In addition, efficacy was seen in all subgroups analyzed.

I will now present the results of the microbiology analyses. Dr. FitzSimmons has already described the importance of Pseudomonas aeruginosa in chronic lung infections in patients with cystic fibrosis. Here are some of the challenges that we faced in collecting and analyzing the microbiology data.

These infections are unusual. In fact, they are chronic and high grade, but localized to the respiratory tract. Colony counts of up to 10_8 CFUs per gram of sputum are commonly seen. Multiple morphotypes of P. aeruginosa often co-infect patients. Each morphotype may contribute in different degrees to

the colony count, and each may have a different level of antibiotic susceptibility.

In addition, other organisms may infect these patients and be associated with the worst prognosis. Thus, in order to study the microbiology of CF rigorously, we have collaborated with Children's Hospital in Seattle to develop our methods for our Phase III studies. Bear in mind that the results I'll present to you were obtained using quantitative sputum cultures and high-level MIC determinations that are not routinely available in clinical microbiology laboratories.

We considered the three key microbiological questions to be: first, does treatment with TOBI change the tobramycin susceptibility of P. aeruginosa? Second, is there an MIC value above which no clinical response to TOBI occurs? Third, does treatment with TOBI change the sputum microbial flora?

We addressed the first question by analyzing the changes occurring at all P. aeruginosa isolates pooled from both studies, and also by analyzing the changes occurring in the most resistant isolate recovered for each individual patient.

These graphs represent the distribution of

the tobramycin MIC of all P. aeruginosa isolates in both the TOBI and placebo groups. The MICs at week zero are represented by the blue line. The MICs at week 24 are represented by the yellow line. The TOBI group is the placebo group. The two curves in the TOBI group illustrate that the tobramycin MICs at week 24 were similar, but not identical, to those at week zero.

The tobramycin MIC 50 and MIC 90 values for all P. aeruginosa isolates recovered at week zero and week 24 are presented in this table. As you can see, the tobramycin MIC values were comparable between the TOBI and placebo groups at baseline. In the TOBI group, at week 24, the MIC 90 increased twofold, one dilution, from eight micrograms per ml to 16. This indicates there is some increase in tobramycin MICs after three cycles of TOBI treatment.

The analysis of the change in tobramycin susceptibility occurring in individual patients confirms the findings and analysis of the P. aeruginosa isolates just presented. For each patient, the MIC at the most resistant isolate in week 24 was compared to the MIC at the most resistant isolate at week zero. Because of the variability of MIC testing, an MIC within one dilution was considered

to be unchanged.

For this analysis, MICs were grouped into six categories -- the lowest, all less than or equal to four, the highest, greater than or equal to 128 micrograms per ml. The majority -- 85 percent -- of the TOBI patients had isolates with MICs that were unchanged or decreased after three cycles of treatment. However, 15 percent of TOBI patients had isolates with increased tobramycin MICs.

In answer to the first question, yes, TOBI therapy for six months does increase the MIC of P. aeruginosa isolates for a small percentage -- 15 percent -- of CF patients. To put this number in perspective, three weeks of cepherofiloxin monaltherapy in CF patients has been reported to result in up to a 100 percent rate of resistance. Two weeks of tobramycin intravenous therapy has also been reported to result in rates up to 15 percent resistance to parenteral therapy.

The second question: is there an MIC value above which no clinical response for TOBI occurs? Patients should respond to antimicrobial therapy at the level of the after drug, if the site of infection exceeds the MIC of the target organism. Toxicity limits the dose of tobramycin that can be

safely given parenterally. Thus, a break point of 16 micrograms per ml has been set for parenterally administered tobramycin.

Aerosolization of tobramycin allows target delivery of high concentrations of the drug at the site of infection. Because of this, we would expect patients to respond to therapy as long as the concentration of active tobramycin in their sputum exceeds the MIC of the infecting organism. Therefore, the parenteral therapy break point does not apply.

To test this hypothesis, we used a measure of tobramycin susceptibility, the MIC at the most resistant isolate from each patient at the start of therapy. We used as a measure of clinical response the change in FEV1 at week 20 relative to week zero. Because of the decline in pulmonary function observed in patients in the placebo group, TOBI patients who maintained or improved their FEV1 were considered to be responders.

The number in each bar indicates the number of patients evaluated in each MIC category. The bars represent the percentage of responders. The percent of responders in each MIC category was not significantly different, as demonstrated by the upper limits of the 95 percent confidence intervals. Even

at the greater than or equal to 64 micrograms per ml category, four of ten patients -- that is, 40 percent -- responded.

No patient with week zero MICs of greater than or equal to 128 micrograms per ml were responders at week 20. However, there are only four patients in this category, and as you can see the confidence intervals are wide.

In contrast, we also examined the predictive value of an MIC at the end of treatment. Again, the bars represent the percent responders in each MIC category. The data indicate that the MIC at the most recent isolate at the end of treatment was not a good predictor of response.

Even at the MIC grouping greater than or equal to 128 micrograms per ml, seven of 15 patients -- that is, 47 percent -- responded. Note that the upper limits of the 95 percent confidence intervals were almost identical across each MIC category.

To answer the second question, with the current data we did not find an MIC above which no clinical response to TOBI occurs. Currently, the clinical response in each patient is the best indicator of the value of TOBI therapy.

The third question: does treatment with

TOBI change the sputum microbial floor? We addressed this question in two ways. First, we analyzed the number of patients who are superinfected with intrinsically tobramycin-resistant pathogens. Second, we analyzed the incidence of recovery of other pathogens, including gram-positive and fungal organisms.

One concern is that patients chronically treated with TOBI will become infected with intrinsically tobramycin-resistant gram-negative pathogens -- in particular, Burkholderia cepacia. This organism has been associated with epidemic spread and can be rapidly fatal in some CF patients. The clinical significance of infection with Stenotrophomonas maltophilia, Alcaligenes xylosoxidans, is not as well established as B. cepacia but is a concern to clinicians.

Superinfection was defined, "On the basis of recovery, the organism at the end of the study would have not been present at baseline." An adverse clinical outcome was not required to be categorized as superinfected.

As can be observed from this table, the TOBI group did not show an increase in number of patients with superinfection.

We also monitored the incidence of isolation of other pathogens, such as Haemophilus influenza, Staphorius, Candida albicans, and Aspergillus species. The recovery of both Haemophilus influenza and Staphorius was decreased in the TOBI group following three cycles of TOBI therapy. An increase in the isolation of fungal pathogens, Aspergillus species, and Candida albicans was observed at week 20. No cases of fungal pneumonia were reported in these studies.

In answer to the third question, treatment with TOBI does not appear to result in clinically important changes in the sputum microbial flora.

Let me conclude by summarizing the answers to three key microbiology questions. First, does treatment with TOBI change the tobramycin susceptibility of P. aeruginosa? Yes. As might be expected with antibiotic therapy, a small percentage of patients with TOBI had organisms with increased MICs. However, 85 percent of patients receiving TOBI had organisms of unchanged or decreased MICs over the six-month study.

Second, is there an MIC value above which no clinical response to TOBI occurs? No. With the current data, we did not find an MIC value above which

no clinical response to TOBI occurs. It is clear that the tobramycin parenteral break point of 16 micrograms per ml does not apply to TOBI therapy.

And, last, does treatment with TOBI change the sputum microbial flora? No. Treatment with TOBI does not appear to cause clinically important changes to sputum microbial flora. The risk of superinfection with Burkholderia cepacia, Stenotrophomonas maltophilia, Alcaligenes xylosoxidans was not increased. Fungal isolation was increased. However, there was no apparent clinical significance to this finding.

I'd like to turn the podium over to Dr. Joanne Quan, who is going to present safety results.

Thank you very much.

DR. QUAN: Thank you, Dr. Montgomery.

Our Phase III trials represent the largest and most comprehensive studies of the safety profile of an aerosolized antibiotic in CF patients. The data that I will present demonstrate that TOBI, given in the intermittent dosing regimen, is safe.

I will present analyses of adverse experiences, serum tobramycin levels, and laboratory measurements, as well as specific analyses of renal function, audiology, and drug-induced bronchospasm.

These analyses are based on the data pooled from our two pivotal studies, including a total of 520 patients who received at least one dose of study drug.

Four of the 520 patients died in these studies. All were in the placebo group and were receiving standard care for cystic fibrosis. All died from respiratory failure attributed to lower respiratory tract infection and cystic fibrosis. Based on FEV1 at entry, three of these patients had severe lung disease. One patient had good lung function at baseline but was later withdrawn for worsening respiratory status and hospitalized shortly afterwards.

The favorable safety profile of TOBI is supposed by the analysis of adverse experiences. As Dr. Ramsey has shown, patients with CF are chronically ill with symptoms from a multi-system disease. It is difficult to separate symptoms due to the underlying disease from symptoms due to a treatment being tested in clinical trials.

This slide shows adverse experiences common in CF. As you can see, the same or fewer number of patients in the TOBI group, and the placebo group, reported these adverse experiences. The same pattern is seen for the majority of adverse

experiences.

Furthermore, two complications of CF -- hemoptysis and pneumothorax -- were reported by similar numbers of patients in each treatment group. I'll show you some specific differences between the two treatment groups in a moment.

Overall, the adverse experiences in TOBI patients were considered less severe than those in placebo patients. The P value reflects an analysis of this ordered comparison. More TOBI patients had mild adverse experiences, and fewer TOBI patients had severe adverse experiences, compared to placebo patients.

Four adverse experiences occurred in significantly fewer TOBI patients than placebo patients. These were fever, anorexia, vomiting, and abdominal pain. The reason for the higher incidence of gastrointestinal symptoms in placebo patients is unclear. However, a lower incidence of fever in TOBI patients might be related to a decrease in pulmonary infection.

In the entire analysis of adverse experiences, only two adverse experiences were reported by significantly more TOBI patients than placebo patients -- voice alteration and tinnitus.

Voice alteration occurred in 33 TOBI patients and 17 placebo patients. Tinnitus occurred in eight TOBI patients and no placebo patients.

To analyze this further, we tabulated by cycle the number of patients reporting the onset of voice alteration or tinnitus. A patient could be counted once in each cycle if a new occurrence was reported. However, a patient could be counted only once in the study total column.

As you can see here, the number of patients reporting the onset of these symptoms decreased with successive cycles of exposure to TOBI. Voice alteration was usually mild and occurred more commonly in the on drug than the off drug period. This symptom may be related to an effect of inhaled particles. DNase, another inhaled therapy for CF, has also been associated with an increased incidence of voice alteration.

Tinnitus is a non-specific symptom and may have many causes, one of which is aminoglycoside toxicity. Of the eight patients reporting tinnitus, none withdrew because of this symptom. All completed the study. Other possible causes were identified for episodes of tinnitus in four patients. Two patients were taking ibuprofen, and two others were taking

intravenous tobramycin concurrently with episodes of tinnitus.

In patients reporting tinnitus, serum tobramycin levels obtained at scheduled times during the study were less than two micrograms per ml. These levels were not necessarily obtained at the time that patients were symptomatic, but the low levels do suggest that systemic absorption was not consistently high in these patients. Tinnitus was transient and was mild or moderate in severity. There was no hearing loss seen in these eight patients by serial audiology testing.

We saw minimal systemic absorption with TOBI. Serum tobramycin levels were low when measured at the estimated peak one hour after the TOBI dose was inhaled. The median serum level of tobramycin in these studies was .91 micrograms per ml at week zero and .94 micrograms per ml at week 20.

These can be compared to the maximum recommended peak level of 10 to 12 micrograms per ml. These are below the maximum trough level of two micrograms per ml recommended for parenteral administration. Furthermore, the serum tobramycin levels were similar in children, adolescents, and adults, as well as males and females.

Dr. Montgomery has just noted that the mean sputum level of tobramycin was 1,200 micrograms per gram. Aerosol administration of TOBI leads to high sputum levels and low systemic levels. The low serum tobramycin levels confirm that the 300 milligram dose is associated with minimal absorption.

The laboratory measurements demonstrate that TOBI is not associated with systemic toxicity. Serial measurements of electrolytes, liver function tests, and hematology tests were obtained. In each case, there were no clinically significant differences in mean values, either between the TOBI and placebo groups or within a treatment group between the beginning and the end of the study.

Let me show you some data on renal function. In TOBI patients, the mean BUN and creatinine levels were very similar at week zero and week 20. In the next two slides, our additional analyses will confirm that TOBI was not associated with changes in renal function.

The number of patients in each treatment group, with increases in BUN of 100 percent or more, was comparable. This was true whether considering increases in BUN at one or more visits, two or more visits, or three or more visits. Only one patient in

each treatment group had a BUN value above 30.

No patients had an increase in serum creatinine of greater than or equal to one milligram per deciliter. Nine patients in the TOBI group and nine patients in the placebo group had increases in creatinine of 50 percent or greater. In the nine TOBI patients, the creatinine decreased at the next visit.

The results of audiology tests show that there was no hearing loss during these six-month studies. Serial audiograms were obtained in 302 patients at 39 sites at which audiology was readily available. Criteria for hearing loss were defined prospectively, and audiograms were read by a single expert audiologist before unblinding of the treatment assignment.

Hearing loss was defined as a bilateral, 15-decibel or greater decrease in thresholds at two consecutive frequencies, when comparing the last exam to the first exam. Frequencies between 250 and 8,000 Hertz were tested. No patients had hearing loss by these criteria.

The presence of preservatives and the osmolality and pH of intravenous preparations of tobramycin may lead to bronchospasm when inhaled. In our studies, we wish to assess whether the TOBI

formulation is safe for delivery to the airways.

In order to determine whether bronchospasm was occurring, we use spirometry to measure changes in FEV1. Note that the change in FEV1 was calculated as a percentage of the value measured before study drug and does not use values of percent predicted.

Spirometry was measured immediately before and 30 minutes after the aerosol dose. Spirometry was measured at week zero with the first dose and at week 20 with the last dose. Testing was done with the last dose to detect whether sensitization might occur after repeated exposure to TOBI.

Bronchospasm was not increased with TOBI. The results at week zero are shown with the TOBI group on the right and the placebo group on the left. The horizontal axis shows the percentage of patients for each treatment group, and the vertical axis shows the percent change in FEV1. This graph demonstrates that the distribution of percent change in FEV1 for both treatment groups was similar. In fact, the median change for the TOBI group was negative 1.8 percent.

The graph is similar for week 20, indicating that sensitization did not occur with repeated exposure to TOBI. These data confirm that TOBI is safe for delivery to the airways.

In summary, the data and analyses support the safety of TOBI in this chronically ill population of CF patients. In our studies, TOBI was associated with a favorable adverse experience profile, low serum tobramycin levels, no change in renal function, no hearing loss, and no increase in bronchospasm. These data show that TOBI, when given 300 milligrams b.i.d. in the intermittent regimen, for 28 days on followed by 28 days off, is safe.

At this time, I would like to introduce Dr. Michael Bowman from Children's Hospital in Los Angeles, who will present his analysis of the benefits and risks of TOBI therapy.

DR. BOWMAN: Thank you, Dr. Quan.

Good morning. I have been asked by the PathoGenesis Corporation to discuss with you my analysis of the benefits and risks of TOBI for patients with CF. My comments are based on my evaluation of the data that we all have seen, my roles and experiences as a CF clinician, and as an investigator in the Phase III TOBI trial. My center was one of the starters in the southwest corner on the first map.

Let me begin by discussing the need for a drug like TOBI. Patients with cystic fibrosis, as

you've heard from Dr. FitzSimmons and Dr. Ramsey, have a chronic, progressive, and unfortunately lethal airway infection. We see it in virtually every patient with CF, and it never goes away.

More than 90 percent of patients with CF die from progressive lung infection and from progressive lung damage from this infection. Thus, patients with CF require chronic therapy for Pseudomonas aeruginosa.

We generally see in our patients a one to two percent loss of lung function annually in spite of the very best therapy that we can give them. Any new therapy that can improve lung function or ameliorate the rate of decline would be an important advancement for our patients.

Unfortunately, our current choices for therapy of Pseudomonas infection are not only limited but inadequate. For years, as you've heard, IV antibiotics -- usually a combination of an aminoglycoside and another antibiotic -- have been used episodically. This therapy is inconvenient and expensive. The cumulative aminoglycoside doses may lead to ototoxicity and, occasionally, nephrotoxicity.

Oral quinolones introduced 10 years ago are initially effective but are limited by the rapid

development of resistance. Furthermore, their use is limited in children. In short, current therapy just isn't good enough.

TOBI has dramatic benefits when put into the context of CF. These studies, which have been summarized for you, were well designed and included more than two percent of all U.S. patients with cystic fibrosis. The treatment effect on lung function of 12 percent is impressive when one considers that most patients with CF lose one to two percent of their lung function every year, even when they are getting the best treatment that we can give.

These treatment effects are greater than have been seen with any previous long-term Phase III trial of any other drug studied in patients with CF. The reduced need for hospitalization and decreased number of hospital days -- three days in six months -- represents a decrease of 36 percent of all hospitalization in this patient group. This would be a real benefit to patients and families who are struggling with this disease every day.

The data suggest that there would be a reduction of four and a half days, or 32 percent, of total IV antibiotic days.

The cost of intensive CF therapy is great.

The cost of outpatient IV antibiotic therapy at my center is about $450 per day, and we are reimbursed about $1,100 to $1,200 per in-patient day for a patient with CF. The national average cost may be higher, but this would represent, if we had decreased usage, there could be significant cost savings.

Let me speak about potential risks of TOBI for a few moments. TOBI was very well tolerated by the patients in these clinical trials. CF patients can be very sick people. But with only two minor exceptions, as you've heard -- namely, tinnitus and voice alteration -- the adverse experiences in the TOBI group were similar to those in the placebo group. These two adverse experiences decreased with time and did not make patients withdraw from the studies.

There are a number of more theoretical issues that we must consider. The microbiological risk factors are of concern. Microbial resistance is perhaps the most significant.

The data shows that only seven percent of patients had MICs equal to or greater than 128 micrograms per ml at six months, and half of those had responded to TOBI therapy. Although longer studies are important, it appears that the rate of loss of efficacy due to resistance is likely to be low.

I would remind you that use of intravenous aminoglycosides is also associated with increasing MICs in Pseudomonas. As many as 15 percent of patients may develop resistant isolates after two weeks of parenteral therapy. The use of TOBI decreases the frequency of IV tobramycin use. Furthermore, the intermittent usage approach is an attempt to minimize this problem of increasing MICs.

The risk to other patients from resistant organisms is low. Pseudomonas aeruginosa CF isolates are adapted to the CF lungs and rarely, if ever, infect non-CF patients. Furthermore, cross infection between patients with CF with Pseudomonas aeruginosa rarely occurs, unlike Burkholderia cepacia where epidemics have been reported.

The mechanisms for resistance in Pseudomonas aeruginosa CF isolates are usually non-enzymatic and few CF isolates have transmittable plasmids that can transfer resistance to other bacteria.

Superinfection did not appear to be a problem. I think that the increased fungal colonization warrants watching, but invasive fungal pneumonia is uncommon in patients with CF, even though more than 20 percent of all patients are colonized.

Aminoglycoside toxicity was not found, but longer term experience, obviously, will be necessary. The respiratory tract risks appear low, since other inhaled drugs, such as DNase, may also cause voice alteration. The concept of intermittent therapy may become common to minimize these risks.

In short, I believe that the safety profile of TOBI is excellent. The adverse experiences can easily be managed and the theoretical risks appear low.

Let me sum up by reiterating that our patients with CF need new therapies for their chronic Pseudomonas aeruginosa infections. I regard TOBI as a powerful and novel approach to the manage of such infections in CF. Most likely it is the first of many antibiotics that will be developed specifically for aerosol administration.

There is clear, statistically significant, and clinically relevant data from these two well-designed studies to support TOBI's safety and effectiveness. The risks are well understood and appear tolerable, especially considering the benefit that patients should derive from this treatment.

These benefits include improved lung function and improved quality of life by avoidance of

hospitalizations and reduced need for IV antibiotics. In my judgment, TOBI is an important new contribution to our ability to treat patients with CF. We who care for patients and families with CF on a daily basis regard TOBI's approval as an important and urgently needed treatment milestone.

Thank you very much.

DR. PITLICK: Thank you, Dr. Bowman.

That concludes our presentation this morning. We hope that in the last hour and a half we have given you an appreciation for what a significant advance in CF care TOBI represents, and we thank you for your attention and ask for your approval.

CHAIRMAN CRAIG: We have time for some questions.

Dr. Norden?

DR. NORDEN: This was really a very clear and nice presentation. The question I would like to ask is, I'm sure, the obvious one. The reduction in Pseudomonas burden falls off. The ability to reduce the load of Pseudomonas falls off. The change in FEV does not. What do you attribute the continued success to, if it's not eradication of the organism?

DR. PITLICK: Thank you, Dr. Norden. We have examined this issue very carefully, and I think

Dr. Montgomery can address the change in sputum bacterial density in the third cycle.

DR. MONTGOMERY: We were plowing new ground using CFUs per gram of sputum in a chronic study. They had only been acutely used for acute exacerbation studies and hadn't been used before. But we do have some correlations between CFUs per gram of sputum and what is going on at week 4 and week 20.

And I believe I need my other book, the red book.

In previous studies, the correlation between CFUs and lung function improvement have been great group, but individual correlates have been pretty poor.

And the slide I'm looking for is -- and I have, in a backup slide -- I'd like to look at the changes overall. And could you please show me Slide E85? And this is at week 4 -- a correlation between relative change in FEV1 and what is going on.

And as you can see, this is for the overall -- both study groups. And as you can see, on one axis here, we have improvement of FEV1 and a relative change -- the absolute change in CFUs. For instance, if you were down two logs in CFUs, about 50 percent, you would be right here at lung function.

This is all of the patients at week 4.

Could you then show me the change for the placebo patients, which would be Slide E88, which would be -- this is both TOBI and placebo. As you can see, the placebo patients are right around a bull's-eye around the axis showing the variability.

And then we'll look at week 4 for the TOBI patients, which is Slide E91, please, and at week 4. And you can see a better correlation. As you can see, most of the patients are lost and improved, showing on TOBI.

And then I want to show you in contrast to what's going on at week 20 -- to answer your question, Dr. Norden -- show the placebo patients at week 20, which would be Slide E90, please. And as you can see, the placebo patients had the trend, as we saw, with decreasing lung function and increasing CFUs.

And then, looking at the TOBI patients at week 20, the correlation would be Slide E93, please. And we have not as nice as in week 4, but we still have the trends that you're seeing.

Now, what is going on here? Is tobramycin doing something else -- decreasing some of the other factors? The MIC is decreasing some of the virulence factors of Pseudomonas, and also contributing to

efficacy? Or are we seeing a change in the sputum because of the efficaciousness of the drug? Are we decreasing the quality and the characteristics of the sputum, therefore, somehow altering this measurement? We just don't know what is going on here, but we do see clinical efficacy.

So I think this is the -- we're sort of in a gray zone here. It's the first time anyone has ever looked at this after six months of therapy, and yet clinical efficacy was clearly well maintained. And the patients clinically, and their responses, were actually maintained, too. They felt better on therapy. So I hope that answers your question.

CHAIRMAN CRAIG: Dr. Parker?

DR. PARKER: I'm asking for the rationale for your selection of this relative FEV1. Specifically, I am -- obviously, why you would want to look at -- or it's obvious why you'd want to look at the difference from baseline to end point. But I'm asking why you feel it's necessary to further adjust for baseline by this division, A.

And, B, given that there is a good reason for doing that, since this is algebraically -- you know, you've got your observed minus baseline, divided by baseline, since this is algebraically equivalent to

having just the ratio of outcome to baseline minus one, why not use that if there's a good reason to do this, rather than have this obscuring minus one?

So I'd be interested as to why we're going through a little flim-flam of divisions and changing our units?

DR. PITLICK: Thank you. There is some historical perspective on why we did that, and Dr. Montgomery can address those issues.

DR. MONTGOMERY: The CF community has conducted studies, and particularly the Pulmozyme studies are probably the most well done large randomized clinical studies, and that's the way it was done. It's sort of the accounting standard in CF.

However, of course, you always look at it the other way. And it doesn't change statistical significance of the results. It just shows the expression difference.

And just to show that, could I have Slide E42, please? And what I have done here on this slide is this is for the 002 study. The curves, as you know, are pretty same between the two studies. Instead of normalizing for the baseline, you can see the effect of TOBI. And this is the absolute FEV1. And there's a small difference in the baseline level

of FEV1 between the two studies, but you can see how TOBI goes up, and so it doesn't change the statistical significance.

So it depends how you want to count. But no matter how you count, TOBI still wins, and it still wins bigger than any previous study ever done. So I think it's just an accounting standard. If we use the accounting standard -- this thing -- and the CF physicians are all used to the DNase numbers, which is improvement -- a relative improvement of 5.6 percent -- and we're using an absolute percentage, there's going to be some confusion.

So we're almost expressing these things just because that's the way it was done in the past, but it doesn't change the answer to the trial at all, how you express it.

Thank you.

CHAIRMAN CRAIG: Just finish up your question. Go ahead, Dr. Parker.

DR. PARKER: You were reporting some P values at the end, and just a question as to -- is this just a plain old T test that you've done at the end there? And these P values reported different between placebo and treated? And was this, you know, done on this mean or this relative change?

DR. PITLICK: I'll have Kelly Otto, our statistician, comment on the statistical test used.

Kelly?

MS. OTTO: Actually, yes. In the NDA that we submitted, we did use the T test for that analysis. However, the FDA requested that we verify our P values that were reported in the NDA using the randomization test. And so the P values that you've seen presented today are from a randomization test with 10,000 permutations. The results were almost identical with that verification.

CHAIRMAN CRAIG: Dr. Azimi?

DR. AZIMI: It was mentioned that there was an increase in the number of fungal isolates after the use of TOBI, and then it was also -- the statement was made that that was of no clinical impact. I always thought that the increase in -- there was some association between clinical disease and colonization with fungi such as Aspergillus, and so forth, in these patients, and that was a big problem. Whereas, here I don't know if you have any more data than what was mentioned here.

DR. PITLICK: Well, we examined pretty carefully those patients with increased fungal infections.

Dr. Montgomery, do you want to address that issue?

Dr. Ramsey will speak to that.

DR. RAMSEY: As far as association with fungal disease, first of all, it is not unusual for these patients to be colonized in their upper airway. And these are expectorated sputums, and so it's obviously passing through the upper airway. It's not uncommon, after IV antibiotics, to see this colonization. Do they have invasive disease?

I think one of the things you are probably thinking about is something called allergic bronchopulmonary aspergillosis, which is a hypersensitivity reaction to chronic Aspergillus infection, which is not what we were talking about here that is diagnosed separately. Invasive disease, fungal disease, is almost unheard of in this disease, and it's usually only in patients who have undergone lung transplants or have been immunosuppressed for some other reason.

So, actually, fungal colonization tends to be extremely benign, and it is rarely treated unless there is other complications that I am talking about. For some reason, the patient has to be immunosuppressed -- the most common being transplant

in this timeframe.

CHAIRMAN CRAIG: Dr. Henry?

DR. MONTGOMERY: Another way of answering the question is: do patients with Aspergillus respond to TOBI therapy? And we can look at that on baseline.

Could I have Slide M36, please? And this is baseline Aspergillus colonization, looking at those people that had a positive clinical response by FEV1 as judged by week 20. And you can see at baseline we had 45 people that had an Aspergillus species. And of those, 53 percent of them were responders, and the once absent 68 percent were responders. So there are still clinical responders in those people with Aspergillus species.

We also looked at the incidence -- the use of antifungal antibiotics during the study and the indications, and there were equal numbers in both the TOBI and the placebo group. And the most common clinical indication was oral thrush.

Thank you.

CHAIRMAN CRAIG: Dr. Henry?

DR. HENRY: I actually have two questions. First, I'd like to start by saying that I see a number of kids with cystic fibrosis, so I certainly support endeavors to find ways to improve their care and their

quality of life and life expectancy.

I know that in the younger age population that Pseudomonas aeruginosa colonization is less frequent. But I'm curious if you broke out the data to look specifically at the young kids with regard to the adverse effects of tobramycin and the effects it would have, for example, on renal function or tinnitus audiology testing, given that you're giving the same dose to a smaller child and the amount of drug per volume of lung or airway that it's being exposed to is much different. And when you break that out into that age group, do you see any differences?

Because looking at a creatinine on average of .9, you know, if you've got a six-year old patient versus someone who is in their forties, I'm not certain how to interpret that.

DR. PITLICK: Right. Well, one of the things we did was look at serum concentrations in those patients. We didn't see a significant difference among age groups.

But Dr. Joanne Quan can address the adverse event profile.

DR. QUAN: We did look at safety in the different age groups. We looked in children, adolescents, and adults, children being between six

and 12 years. The adverse experience profile was very comparable to that seen in adults, as was seen among all age groups. And, really, the results of all of our analyses were very similar among all of the age groups -- that there was no difference that was seen.

The serum tobramycin levels were also roughly very similar, so it did not appear that there was any different safety profile with a younger age group. Most of the patients who experienced tinnitus were 18 or older, and there was only one patient of those TOBI patients under 18, and she was 15 years old. So none of the children experienced tinnitus.

DR. RODVOLD: Can I ask a question that maybe follows that up? You used serum creatinine changes of one and greater. I was just wondering if you had ratcheted that data down to like .5 and greater, or a 50 percent change in --

DR. QUAN: Actually, we did look at it.

DR. RODVOLD: You did? Okay.

DR. QUAN: We did look at changes of 50 percent or greater.

DR. RODVOLD: Okay.

DR. QUAN: And there were nine patients in each treatment group.

DR. RODVOLD: Okay. Thank you.

DR. HENRY: I guess the other question I had that relates to tobramycin usage -- of the people entered in the study, I know that they weren't allowed to enter the study if they had had antibiotics 14 days prior. But what was the usage of tobramycin in the patient population prior to being in the study? And was there concurrent use of tobramycin systemically when they had exacerbations? And how might that have affected their results?

DR. QUAN: It was very common for patients prior to enrollment in the study -- and, actually, in the several months prior to them being screened for the study -- to use tobramycin, since septazanime and tobramycin is the most commonly used anti-pseudomonal antibiotic combination used.

Roughly -- let's see, I can show you -- when we looked at concomitant medication use during the study, it is not surprising that more patients in the placebo group used tobramycin during the course of the study.

Let me have Slide S179, please. This slide tabulates any use of intravenous aminoglycosides in tobramycin during the study. And as you can see, roughly 38 percent -- 37 or 38 percent of the patients in the TOBI group used aminoglycosides, mostly

tobramycin, and about half of the patients in the placebo group used aminoglycosides. And most of that use was tobramycin, and that difference is statistically significant.

DR. HENRY: Thank you.

CHAIRMAN CRAIG: Dr. Prince?

DR. PRINCE: While you're talking about resistant organisms, I think one of the concerns has been that this is a very useful drug in cystic fibrosis, and that if everybody starts using it every month it will have widespread resistance. I had a couple of questions.

First of all, how much cross resistance do you see to other members of the aminoglycoside family? In your group that would have been conventionally resistant to tobramycin, are those all amikasin-resistant as well?

DR. PITLICK: Thank you. I'd like to have the microbiology group answer that question.

Dr. Garber?

DR. GARBER: Could I have Slide M18, please? What I'm showing here is a slide indicating mechanisms of resistance with analyzed strains with a high MIC from both the placebo and TOBI group. And if you'll look in the columns marked with blue, these are

typical isolates of Pseudomonas aeruginosa taken from hospitals.

George Miller has been surveying these for the last several decades, and about 30 percent have this permeability defined classification resistance, which is a broad aminoglycoside resistance. And what you see is about 30 percent of his showed that, and 70 percent showed the standard enzymatic and activation mechanisms.

What we have observed -- and others have seen this in the past in our trial -- is that over 90 percent of ours show this permeability mechanism, whether in the placebo group or the tobramycin treatment groups. We haven't changed anything by the treatment, and that type of mechanism is broadly resistant to all of the aminoglycosides.

DR. PRINCE: If you take the group of patients that had conventionally resistant isolates, and look at them after you've totally stopped tobramycin therapy, what happens to those MICs? So a month off therapy at the next time they are cultured, if they had an MIC of 16 at week 20, what happens at week 24 or at week 40? Do you know that?

DR. GARBER: If I -- you're talking about the stability of the --

DR. PRINCE: For example, with the floraquinolones, the concern was that they would step wise very slowly over a predefined ratchet, up and up and up.

DR. GARBER: Right.

DR. PRINCE: And not drop back down to a susceptible level. I was curious if you had looked at that with these isolates.

DR. GARBER: What you see in sampling patients over the course of the trial is that the levels go up and down. In terms of the highest MICs, we see the highest density isolates.

DR. PRINCE: I was just curious if you had data afterwards, after you've stopped tobramycin and they hadn't seen the drug again for a period of time -- whether the MICs stayed high or whether they went back down.

DR. MONTGOMERY: Well, I guess the best example is -- could you give me Slide M4, please? We'll show you some data.

What we've done here is looked at -- week zero is the baseline of study, week 20 is the end of the third on drug period, and week 24 is four weeks off. So you can sort of see what is going on.

I have split up the isolates into three

categories -- all isolates; the highest MIC isolates, which are often not the most dense; and then the highest density isolates, so we can actually see what is going on. And if you can see, in the all isolates, you see the change, as we noted before, the twofold increase at week 20 which is maintained.

If you look at the highest MIC isolates, which is taking the worst case look, it does go up and there is some reversion back between week 24 and week 20. So you have the twofold change there. And the highest density isolates, you really don't see that. So there is, as you can see, some trend here for reversion in an off drug period.

CHAIRMAN CRAIG: Thank you.

Dr. Reller?

DR. RELLER: Since 37 percent of the TOBI group received that parenteral tobramycin, and 48 percent of the placebo group, do you have what the shifts in MICs were within each group for those who received and those who did not, to put the issue of the small shift in MIC, and those who received TOBI, as to whether or not that shift was greater in those who got both parenteral and inhaled tobramycin versus those who were in the placebo group?

DR. MONTGOMERY: You're asking us, do we

know what is the percentage of the shift on people that were on TOBI alone and also on IV plus TOBI, is that -- that's your question?

DR. RELLER: Relative to the placebo.

DR. MONTGOMERY: Okay.

DR. RELLER: I'm wondering if the exposure to parenteral tobramycin isn't perhaps a bigger factor than whether or not there is exposure to inhaled.

DR. MONTGOMERY: Okay.

DR. RELLER: Or whether getting it both ways amplifies things.

DR. MONTGOMERY: Could I have Slide M8, please? I don't quite have your answer, but I think I'm close. So we'll see if this suffices.

What I've done here is done kind of a worst care analysis of looking at the worst MIC -- week 20 or week 24, because there is some variation -- versus week zero, and looking at all patients in the TOBI group, 25 percent, and then in the placebo group, which is 10 percent. And I have the -- and then I looked at the number of patients with no IV aminoglycoside exposure.

And let me march through the numbers here, how this 25 percent is derived. Fifty-seven of the 231 patients showed shifts in the range that we

thought to be clinically relevant. And you look in the placebo group, we had 22 out of 224.

However, when you look at the no IV aminoglycoside subset, you're at -- the TOBI group has 32 of 143, or 22 percent, and the placebo group, 11 of 109. So, in this analysis, we do have some -- there is some baseline variability going on. So even in the placebo group, we have some going up in spite of no antibiotic pressure. And it shows, I think, there is some inherent variation in the phenotype of these organisms.

But I think most of the -- most of the effect, I think, is actually due to TOBI, not due to IV antibiotic exposure, would be my answer.

Does that answer your question?

DR. RELLER: It gives a hint. We don't have the actual numbers that we'd like to see. But you think, actually, that the --

DR. MONTGOMERY: I think it's the TOBI --

DR. RELLER: -- tobramycin may have more of an effect than the --

DR. MONTGOMERY: Yes, it's the inhaled -- I'm not going to deny it. It's the inhaled that is probably causing most of the effect here.

DR. RELLER: The MIC determinations were

done on twofold dilution steps, with ager dilution methodology or --

DR. MONTGOMERY: Jill Van Dalfsen will answer the methodology question on that.

Jill?

MS. VAN DALFSEN: We used the broth microdilution method, using a sensititer system. So they were incubated for 18 to 24 hours and read manually.

DR. RELLER: On twofold dilution steps.

MS. VAN DALFSEN: On twofold dilutions. Yes, that's correct.

CHAIRMAN CRAIG: Could I ask if you looked at any of the organisms as for multiple mechanisms of resistance? The question is, is how high is the highest MIC that you get with permeability? Usually, what you start to see with those organisms is you keep getting their MIC up, because they really start growing very slow and start being real cripples.

And so I wonder, when I look at your data, I see the little blip which tends to be in your distribution curve right around eight or 16. And so my question is: are those that are higher transport mutants that have also some other mechanism of resistance? And so that, really, all we're going to

see is this collection right around 16 or 18. And if they get higher, we're going to end up with wimps.

DR. GARBER: The permeability mechanism -- and we don't understand biochemically what that means; it's a functional definition -- is found in conjunction with enzymatic mechanisms. But, in fact, we've never seen enzymatic mechanisms really powerful enough to inactivate the drug at the level that they are receiving in the lungs.

So every case in which an organism has achieved the higher level of resistance -- and we have measured some of these now under research conditions, not under our standard screening conditions, up to 2,000 micrograms per ml mechanisms, and those all have this permeability feature.

CHAIRMAN CRAIG: Yes?

MS. ALTAIE: This is Sousan Altaie, FDA.

As I was standing here waiting for my turn, most of my questions were answered. But I still have the concern that we did see the pulmonary function decline as the colony-forming units inclined. And I wonder what happens -- my concern is what happens after that 20 weeks. Are they going to reach each other and pulmonary function goes back to the baseline numbers, goes back to the baseline?

And the numbers that you were showing us between 20 weeks and 24 weeks also showed that the scattering of the less numbers are going toward the cluster in the center where like the placebo was. So that trend was very obvious there. And I'm kind of concerned, and I was wondering if you could address that concern I have.

DR. PITLICK: Is your concern about what happens between week 20 and week 24?

MS. ALTAIE: No. The trend that the colony-forming unit goes up, and you nicely demonstrated that you're not touching the rest of the flora that we're wondering about -- the cepacias, the xylosoxidans, the other -- the organisms that are there -- staph aureus. Those are not being touched.

So the difference, I would imagine, is the Pseudomonas. And as you go with cycle after cycle, at 20 cycles you're closing that gap of the difference between both measurements -- pulmonary function and the colony-forming units -- and that concern still remains. What happens after the 24? Are we going to have no effect?

DR. PITLICK: Well, there are two things. First of all, our effect at week 20 is still a 90 percent reduction in the number of bacteria in the

lungs. That is not trivial. That is a huge reduction in bacterial density. So while it doesn't look very great, it is still significant. And pulmonary function is maintained above baseline for extended periods.

Dr. Montgomery?

DR. MONTGOMERY: The data we presented today are for the indication requested. We have open label experience studies for one-year additional experiences that are ongoing, and we're reporting these studies to the FDA. And at the request of the FDA, we agreed to only present data included in the NDA at this meeting.

The only data we have for longer experience in the NDA reflects the data and some patients we included in an open label follow on. And those were 68 patients which were followed on out. And this does not represent the total number of patients that we have seen, and I don't -- John, are you going to show that data later, or not?

DR. ALEXANDER: There will be a brief slide later on.

DR. MONTGOMERY: Brief slide. Well, I'll steal John's thunder --

(Laughter.)

-- and basically say that in a small analysis treatment effect was maintained. And treatment effect was maintained in those patients for the time. So our preliminary indication does not support, you know, the fear that we're losing efficacy over at least a year.

Thank you.

CHAIRMAN CRAIG: Dr. Henry?

DR. HENRY: I'll make this very brief.

Compliance is a major issue, as anyone who takes care of CF patients knows, especially in the adolescent population. Obviously, it is better to give something twice a day than three times a day, but what happens if it's only given once a day, despite the fact it doesn't take very long to administer it? What happens if it's given once a day? And was any attempt made to give aerosolized TOBI in some set relationship with bronchial drainage?

DR. PITLICK: Well, we can't really answer that, since we only studied it twice a day. So --

DR. HENRY: So no preliminary information. Everyone who took it took it twice a day as --

DR. PITLICK: That's correct.

DR. HENRY: Okay.

CHAIRMAN CRAIG: No believers in the post-

antibiotic effect, huh?

(Laughter.)

DR. HENRY: And was there any association with how it was administered in relation to bronchial drainage?

DR. PITLICK: Are you speaking about the order of treatments?

DR. HENRY: The order of treatments, yes.

DR. PITLICK: Okay. The order of treatments was that TOBI was always administered last. So all of the treatments were administered prior to TOBI, including bronchial drainage.

CHAIRMAN CRAIG: Yes, Dr. Danner?

DR. DANNER: In terms of your tobramycin concentrations in the sputum, how fast do they fall after treatment?

DR. PITLICK: From previous studies, it appears that the half-life in sputum is about two hours, so that within six hours there are negligible amounts in the sputum that we can detect.

CHAIRMAN CRAIG: Okay. Let's take our break, and exactly in 15 minutes we'll restart. We're a little behind, but I thought it was good for us to get these questions from the panel. It will probably make the discussion go quicker.

(Whereupon, the proceedings in the foregoing matter went off the record at 10:25 a.m. and went back on the record at 10:40 a.m.)

CHAIRMAN CRAIG: All right. Take your seats.

The next presentation will be by Dr. Alexander, the FDA efficacy analysis.

DR. ALEXANDER: Good morning to members of the committee and to everybody in the audience.

My name is John Alexander, and I am here to present the efficacy results of the FDA analysis. Mine is the first half of the FDA presentation, and after myself Dr. Marianne Mann will give a presentation of the safety results. So, in effect, I get to sort of tell you the good news and she gets to tell you the bad news.

I would, first, like to thank Dr. Stacey FitzSimmons for her presentation of the CF registry data, and Dr. Bonnie Ramsey and the sponsor representatives from PathoGenesis for their presentations. It allows me to sort of focus my presentation more on what I think are pertinent results.

So my presentation is going to focus on

the two pivotal trials -- PC-TNDS-002 and 003, Phase III placebo controlled clinical trials to study the safety and efficacy of tobramycin solution for inhalation in patients with cystic fibrosis.

PathoGenesis has already given you a pretty thorough overview, so what I'm going to do is start by highlighting some important features of the study design itself and then go on to the study results.

Next slide?

A complete list of the inclusion and exclusion criteria are available in the briefing package that was provided to you, but I wanted to make some important points as to some limits in the inclusion criteria. First of all, we are talking about patients who are greater than or equal to six years of age. And this limitation, as mentioned earlier, is basically related to the problems of measuring PFTs in children that are five years of age or younger.

The second -- an FEV1 of less than or equal to 75 percent, or greater than or equal to 25 percent of predicted based on gender, age, and height, using the Knudsen equation. When you look at this, it is important to note that with this exclusion criteria

you are limiting the children to children who have more severe disease.

The CF registry data that was provided by Dr. FitzSimmons showed that approximately 40 to 50 percent of children in the youngest age range, six to 12, actually have FEVs that are 70 percent or greater. So that's an important point to make -- that we are actually excluding about half of the youngest children who were eligible for this trial by age using this FEV criteria.

The third thing that is important to note here is that we're talking about Pseudomonas aeruginosa, patients with Pseudomonas aeruginosa present in sputum or throat cultures within six months prior to the trial and at a minimum of one of the screening visits.

So this trial is a trial that studies the effect of using tobramycin on those patients who are already colonized and known to have Pseudomonas present. It doesn't relate to the approximately 20 percent annual incidence of new Pseudomonas aeruginosa, and it doesn't deal with the acquisition of Pseudomonas aeruginosa in patients.

Next slide?

The most important of the exclusion

criteria, I think, is this one related to having a history of Burkholderia cepacia. So those patients who had a history of a sputum culture or a throat culture yielding B. cepacia in the previous two years, or who had B. cepacia at one of the screening visits, were excluded from the study.

And I think that that is an important point to make -- is that in designing these clinical trial, there was concern about the possibility that the use of tobramycin might cause worsening illness in these patients who are already known to have a worse prognosis, because of the presence of this organism.

Next slide?

In dose selection, the sponsor has already discussed the dose used in the pivotal trial and the rationale for this particular dose, trying to get the organism to be -- I'm sorry, trying to get the drug sputum concentration to be at a point that is above 10 times the MIC 90 for most of these organisms.

Next slide?

This histogram shows, then, the distribution of the sputum concentrations that were measured in the pivotal trials -- PC-TNDS-002 and 003 combined. And so what you see is that they do, in fact, achieve the peak sputum concentrations that they

were looking for. The mean is a little less than 1,200 micrograms per gram of sputum, and the median is a bit lower than that, as you'd expect given there is a positive skew of the data.

Next slide?

But the problem is that with the lung we are dealing with somewhat of a black box phenomenon. You have aerosolized drug that is being administered and going in.

Next slide?

And from the black box, we obtained sputum cultures, sputum drug concentrations on what is expectorated, and pulmonary function tests, which give us some idea of the function of the box.

Next slide?

But what is going on inside is still something of a mystery, especially as regards the lung distribution of the tobramycin as it is aerosolized, the effect of the drug on Pseudomonas in the lower airways, and its overall mechanism of action.

Next slide?

So this is, briefly, another review of the study design. The patients had two screening visits -- visits 1 and 2 -- and then at visit 3, which is also week zero, is when the patient started on drug

therapy. And they received 300 milligrams of aerosolized tobramycin twice a day for a period of four weeks, then were off for four weeks, on for four weeks, off, on, and off.

The baseline measurements were those that were taken at visit 3, and one important point to note is that the end point that was chosen by the sponsor was here at visit 10, which is not the end of the trial or the end of the third cycle, but rather the middle of the third cycle, which is when they had just finished a month of tobramycin therapy.

Next slide?

So let's look at the study results. Okay. So you know that slide that everyone has with the tiny little numbers that nobody can read?

Next slide?

(Laughter.)

This is it. My basic point in showing this slide is that there were several demographic variables that were stratified and other demographic variables that were seen that were equal in the two treatment arms in each protocol, so that the TOBI patients were comparable to the placebo patients in each of the two trials.

The other point, though, is that also in

comparing across the two trials, we didn't really notice anything that was different in terms of these baseline demographics from one trial to the other, and that's going to become important later.

Next slide?

So we looked at the primary efficacy end points, and these are the end points that were chosen by the sponsor -- mean relative change in percent predicted FEV1, absolute change in the logs of the colony-forming units per gram of sputum as measured by a quantitative sputum culture, and also the mean relative change in percent predicted FVC.

Next slide?

So we asked the question: what exactly is a mean relative change in percent predicted FEV1? And being a pediatrician, not a pulmonologist, I sort of struggled with this in the beginning as to try and figure out exactly what this represents and a good way to represent the data to people who aren't pulmonologists so they could understand.

So what happens is that at each of these visits -- visit 10 and visit 3 -- the patient has a percent predicted FEV1 measure. The percent predicted FEV1 at visit 10 is taken, minus the baseline percent predicted FEV1, and then that number is divided by the

percent predicted FEV1 at baseline.

And this sort of gives you a percentage -- a difference of a percent of a percent, to give you the relative change in percent predicted FEV1. And once you have this relative change for each patient, then you can figure out what the mean is for that change.

Next slide?

Some important points about this mean relative change is that it has the tendency to inflate absolute changes from the baseline value, since you are dividing by a percentage -- say, 50 percent or 35 percent as a baseline. It sort of increases the absolute change that is present.

The other point about the way that this was calculated is that the results only look at the baseline and the end point data, so that they have data from visit 3 and visit 10 that is included in their analysis, but it doesn't really look at the other points that are there in between.

Next slide?

So why not use raw FEV1 for comparison? The problem is that looking at this, which is the raw FEV1 data by age, you can see that the data is much different for children who are six to 12 years of age

as opposed to adolescents 13 to 17, or those who are 18 or older. And so this will introduce -- this is a part of the problem with the intrapatient variability in the study and in these statistics, to use them.

Next slide?

But this looks at the FEV1 percent predicted, and this is between the two for the protocol 002 and for protocol 003. And, overall, when we looked at the FEV1 percent predicted data by age, you sort of see that all of the patients fit into about the same area at baseline. So that, overall, this represents at least a little bit of a better look at what the average data -- the variability is a little bit less.

So what we have here is that for patients who received tobramycin, they start out at a baseline level about here, and then at visit 10 they are up at this point over here.

The important point that I wanted to make with this slide is that what the sponsor represents as an approximately 12 percent change in -- a 12 percent mean relative change in FEV1 for the TOBI group actually represents a change of about six percent in the percent predicted FEV.

Okay. Next slide?

So that what you see as an approximately 12 percent treatment effect report is approximately a change of six percent in the percent predicted FEV1. And the eight percent treatment -- approximately 8.7 percent treatment effect that was reported for study 003 represents about a four and a half percent change in the percent predicted FEV1.

Next slide?

This slide shows the change in percent predicted FEV1 over the period of the study. And you do see that you have this elevation which is different from the patients who received placebo. And looking at these confidence limits, you can see that there is a difference from the tobramycin group versus the placebo group.

Next slide?

And this slide represents the same thing for study 003.

Next slide?

But the point that I'd want to make here is that in this slide we're looking at what the median values are for FEV for each group and the quartiles. So that these lines don't represent confidence limits out here, but what they actually represent are the upper quartile and the lower quartile.

And what I'm pointing out here is that, overall, the change that we're seeing is a difference between the two studies that is statistically significant, still falls within the level of variability that is seen for each patient, so that it's hard to really identify that patients are having this treatment effect.

This is just another way of showing that same data. What we have is the histogram that shows the change in percent FEV of baseline over the period of study. And this is for protocol 002. It's fairly similar for protocol 003.

But what you see is that, overall, most of the patients still fit within the same area. You do have an indication that the histogram does shift over towards the right, towards more of a change for the tobramycin group. But, again, it's difficult to see a clear separation between the two groups.

Next slide?

This is getting on to the next point, which was brought up earlier. These are slides that show the absolute change in the log CFUs per gram of sputum that were measured. And we were concerned about the same thing that was brought up as a question by one of the committee members -- was that you do see

this sort of trend towards a decrease in effect.

Next slide?

That is seen in 003 especially and 002 a little bit less. But we do have difficulty with understanding exactly what this means, and we don't have data that speak to this farther out in the open label trial.

Next slide?

So now let's move on to looking at some of the secondary end points.

Next slide?

In lower respiratory hospitalization, these were the sponsor's results as they were shown. The percentage of subjects that were hospitalized were reported as 37 percent for TOBI versus 45 percent for placebo, and they gave you an overall relative risk and a P value that was based on the confidence limits that they developed for that relative risk.

And, overall, they did show that for the mean days of hospitalization there were fewer mean days of hospitalization for TOBI patients as opposed to placebo.

Next slide?

In our analysis, with the Kaplan-Meier curve, which is -- this is basically the same curve

that they had shown upside down -- what we see is TOBI is here in red, and the placebo is here in blue -- that, overall, for the time to lower respiratory hospitalization, although there is some indication that the hospitalization is less for tobramycin than it is for placebo, the P value that we obtained with the Wilcoxon test is .11, which is not statistically significant.

Next?

One point that we did want to make is that when separating these data into the two different protocols -- protocol 002 and protocol 003 -- is that we see a difference between the two protocols. So, in protocol 002, what you see is this fairly large difference in hospitalization, as opposed to protocol 003 where both look fairly similar.

Next slide?

When we look at this in terms of subtracting one of those lines from the other and creating confidence limits around it, you see that there is a statistically significant difference in hospitalization in protocol 002. But protocol 003 basically shows that they are the same.

Next slide?

The sponsor's data on hospitalization by

protocol is basically similar. They do find an effect that is present in protocol 2, where 28 percent of TOBI patients versus 45 percent of placebo patients are hospitalized. And, in 003, they find a 43 percent hospitalization rate for TOBI versus 45 percent for placebo. And their relative risks show the same difference, so that there is a statistically significant difference for 002 and a not statistically significant difference for 003.

The same effect is seen in the mean number of days hospitalized by protocol, so that in protocol 002 you see this difference that is statistically significant that is enough to bring the value for the patients in protocol 003 over when you look at the pooled data.

Next slide?

So, next, we take a look at the data for antibiotic use. And, again, the sponsor's results here were for the pooled studies as shown, 39 percent of TOBI patients versus 52 percent of placebo patients, with a relative risk of .64 and a P value that is based on this confidence limit.

The mean number of days of antibiotics were statistically significantly different, with 9.6 days for TOBI versus 14.1 days for placebo.

Next slide?

When we look at the Kaplan-Meier curve, you do see a wider difference here than you did for the patients who were hospitalized. And by the Wilcoxon test, you do end up with a statistically significant difference between those lines in terms of the incidence of antibiotic use.

Next slide?

But, again, when we separate by protocol, you have a much larger difference in protocol 002 and a smaller difference in protocol 003.

Next slide?

And then, when we look at those differences in terms of subtracting TOBI from placebo and developing 95 percent confidence limits around it, you see a statistically significant difference for 002, and a difference that is not statistically significant but is fairly borderline for 003.

Next slide?

The data given by protocol by the sponsor shows, basically, the same type of information, so that we have a statistically significant difference that is seen in protocol 002. And for protocol 003, the difference is less, so that, again, they end up with a borderline result when you look at the upper

end of the confidence limit for their relative risk -- 1.045.

So, at this point, what we have is a question as to why there is a difference between the two protocols. The protocols were initially designed to be identical and to have their results pooled. The exact same protocol was used for study 002 as was used for study 003, so that there shouldn't have been any differences related to different design.

Next slide?

So we started to try and take a look at other things that might have an effect on the hospitalizations, and the two different trials, and on the antibiotic use. This is a slide that shows hospitalization by calendar date in order to try and see was there a difference in the time of hospitalization, was there some sort of epidemiologic phenomenon that was going out, some type of outbreak that occurred at a different time that affected the study results for 003 as opposed to 002.

As you can see here, the studies basically had hospitalizations occurring over the same period of time in the same year, and that we don't see any evidence that there is really a peak difference of when hospitalizations were occurring in one study

versus the other.

Next slide?

I'm not sure if anybody can see that, but there are a lot of pink and blue dots that are all over this slide -- the geographic distribution -- trying to take a look at if there were really any differences between protocol 002 and 003.

There are, of course, some little pockets, like up here in the upper northwest, where study centers that were involved in 002 -- in New England, there is a little bit more of some clustering of 003 centers. But, overall, the distribution of centers for each of the protocols is fairly wide, and we don't see something that is distinct as an area that might have been more effective in one study versus the other.

Next slide?

So, then, we're left with the question of center effects. And, unfortunately, with this study there were 29 centers that were in protocol 002 and 40 centers that were in protocol 003. So that each individual center didn't include enough patients so that an individual center might make a difference.

Whether there are some other differences in terms of the organizations of the overall centers

that we're not recognizing here is a question, but overall we can't really see anything that would result in this difference in treatment effect between the two studies.

Next slide?

Now we'll move on to the subset analyses. And these were analyses that were done by the sponsor -- I'm sorry, by the FDA on taking a look at the baseline demographic criteria the sponsor had separated by -- so one of the points that I wanted to make is that when we talk about lower -- when we talk about hospitalization here, we are talking about lower respiratory hospitalization.

There were approximately seven to eight percent of patients in both the TOBI and the placebo arms that were hospitalized for other reasons -- about two to three percent for GI causes alone, two to three percent for upper respiratory tract infections, including sinusitis, and about two to three percent for other procedures, like surgical procedures, pick line placement, g tube placement, and such.

So what we tried to do was take a look at lower respiratory hospitalization in order to try and eliminate some of that.

One of the important things to point out

is that these are post hoc analyses. These aren't analyses that were meant to -- that the sponsor had originally planned. And so the only thing that we're really seeing here is trends that I wanted to point to.

First of all, for hospitalizations, when you look there is a slightly greater hospitalization in the placebo group as opposed -- in the youngest placebo group as opposed to the older patients. So there is some indication that children get hospitalized a little bit more. But, overall, the difference that we're seeing for TOBI, in terms of its effect, seems to be greater in the youngest age group as opposed to the older patients.

Next slide?

The same type of result is seen in the IV antibiotic use slides, where there does seem to be more of an effect for tobramycin in patients that were six to 12 years of age as opposed to the older age groups.

Now, when I looked at the -- when we looked at the original baseline demographics, what I pointed out was that the inclusion criteria had patients who were between 25 percent and 75 percent of the percent predicted FEV1 at baseline. And so, is

this representing an effect on more severe patients, or is it representing an effect on less severe patients?

Next slide?

What we actually see in terms of hospitalizations by baseline FEV is that those patients who had a baseline FEV that was lower -- less than 50 percent, which is the stratification variable that the sponsor used -- showed not really much of a difference in terms of hospitalization, as opposed to those patients who were greater than 50 percent where a difference was seen.

Next slide?

In terms of antibiotic use overall, the difference becomes less, and I think part of that is just the fact that these patients who have lower FEV1s are the ones who would tend to be the patients who have pick lines or other means of receiving IV antibiotics at home.

Next slide?

Time to lower respiratory hospitalization by DNase use, and I think that this is important to point out -- that what we're seeing is that even though we have a fairly small number here, so that it's difficult to tell trends with the Kaplan-Meier

curve, it seems that the placebo patients actually do a little bit better than the TOBI for those patients who had no DNase use. Whereas, for those patients who did have DNase use, the effect is sort of the reverse.

Part of the question is whether the -- just the fact that this small number of patients is included sort of alters these results.

Next slide?

For antibiotic use, we can see the same thing -- that the lines are fairly close for the TOBI and placebo patients and they cross. Whereas, you see a much wider difference for those patients who are using DNase, so that there is some indication that those patients who receive tobramycin, who also receive DNase, may do better.

This is reassuring in that we don't have to worry about some evidence of the opposite -- that there is some interference between the two drugs that would lead to less effectiveness of the TOBI in patients who are already receiving DNase.

Next slide?

Timed antibiotic use by -- sorted by baseline MIC is shown here. And, again, what we have here is a very small number of patients, so that it is difficult to interpret, at this point, just what this

sort of strange configuration for the Kaplan-Meier curve means. And that's a difficulty that we have in interpretation of the results of all results for patients with sort of higher MICs.

It is difficult to say whether there is actually a treatment effect going on, or whether there is -- whether the patients who have higher MICs are actually still about the same.

Next slide?

Another important point that I wanted to make here is that for low respiratory hospitalizations by gender, we are also seeing a difference between male and female. Now, again, we're getting into a lot of post hoc subset analyses, but there is a question as to whether the gender gap that was noted previously by Dr. FitzSimmons may be partly what is responsible for more of an effect seen in females as opposed to males.

Next slide?

The same results are, again, seen for antibiotic use by gender, where there seems to be a larger effect among females than there is among males. And what you see is that the placebo line here is actually lower than the placebo line for males, whereas the TOBI is about the same.

Next slide?

A couple of additional analyses that we did was to take a look at patients by prior hospitalization within the six months before the study began, or before the patient began study drug, and by prior antibiotic use. And both of these things were codified by the sponsor.

It only includes patients who are included in the six months prior to the trial, so it doesn't discuss hospitalizations that occurred a year before or two years before. And what we see is actually more of an effect for those patients who did not have prior hospitalization as opposed to those patients who were hospitalized previously.

As would be expected, those patients who had previous hospitalizations were the ones that tended to be worse, and you'd kind of expect that the patients who end up hospitalized repeatedly over a six-month period are the ones who are going to have more hospitalizations overall.

Next slide?

In terms of IV antibiotic use by prior antibiotic use, again, we're seeing that those patients with no prior antibiotic use seem to have somewhat of a wider difference than those patients who

had prior antibiotic use. And, again, those patients who had prior antibiotic use are the ones who were usually more severe.

Next slide?

This last part of the analysis done by the FDA was to look at organisms with high MICs, to take a look and see if we could see any evidence of an effect. And we took a look at patients with Pseudomonas aeruginosa with elevated MICs, as well as taking a look at patients with Stenotrophomonas maltophilia and Alcaligenes xylosoxidans at baseline.

Again, it is important to note that patients with Burkholderia cepacia were not included in this trial, so that we can't really take a look, then, at baseline. And another point that I wanted to make is that the data that I'm looking at is for those patients who had MICs that were elevated at baseline. The data regarding increases in MICs are going to be covered in the safety review by Dr. Mann.

Next slide?

What this slide takes a look at is the changes in FEV1 measured as the TOBI patients minus the placebo patients. So that's what this line represents is the change in FEV for TOBI minus placebo, and then we have 95 percent confidence limits

around it. And what you're seeing here is on the X axis is baseline MIC.

So here we have the patients with the lowest MICs and here we have the patients with the highest MICs, in order to try and take a look -- to see if there was any sort of definite break point where this crossed zero, and that patients who were on TOBI showed some worsening. And what we see is that, overall, those patients with the very lowest MICs have the greatest effect. Those patients with a somewhat higher MIC range have somewhat of a lower effect, but the effect is still there.

As we get out farther, we're still seeing that effect, but the question is that our confidence interval becomes so wide that it crosses zero, so that we can't really say very well for patients who have MICs of 128 or 512 what kind of effect that they are actually going to get.

Next slide?

In terms of days of IV antibiotic use, we see the same thing. So for TOBI minus placebo, what you have is that the days of IV antibiotic use are still fairly less as the MIC increases. But you see this sort of widening which crosses zero, so that for those patients with higher MICs of around 64, 32,

we're not necessary sure that there is that effect remaining. But what we don't see is that we don't see a clear line that says this is where we should set a break point for the MIC.

Next slide?

This slide shows the percent change in FEV in liters for subjects with Stenotrophomonas maltophilia at baseline. And, again, the pink line represents patients with tobramycin, and the blue line represents patients on placebo.

Now, we're talking about a fairly small number of patients. There are 18 patients with Stenotrophomonas at baseline in the TOBI group versus 14 patients with Stenotrophomonas at baseline in the placebo group. What I was concerned about is that what we're actually seeing is that for patients with Stenotrophomonas at baseline, their FEV seems to do worse than the placebo group, even though we're talking about a small number of patients.

In terms of antibiotic use and other factors, you can't really tell that much of a difference. For this patient group with Stenotrophomonas, there were eight patients out of 18 who required antibiotic use during the study, and five patients out of 14 of the placebo group who required

antibiotics.

But I think that, overall, it is concerning that there is some evidence that the patients with Stenotrophomonas at baseline seem to do a little bit worse than placebo, as opposed to --

Next slide?

-- the patients who had Alcaligenes at baseline. In this, you see that the tobramycin effect is over that of placebo.

Again, we're talking about small numbers of patients. There were 15 patients in the TOBI arm with Alcaligenes at baseline and 10 patients in the placebo arm with Alcaligenes at baseline. In terms of antibiotic use, there was fewer antibiotic use in the TOBI group, with four out of 15 requiring antibiotics during the trial in the TOBI group and nine out of 10 requiring antibiotics in the placebo group.

Next slide?

Again, one of the small slides with little numbers, but what I wanted to point out here was that the sponsor tried to make some quality of life assessment for these patients by asking either the patient or the parent to give an assessment of the treatment at each cycle. And so this is for cycle 1, this is for cycle 2, and this is for cycle 3.

And when the patients were asked, basically, "How do you think you've done? Has your disease improved, remained unchanged, or worsened?" statistically significantly more of the tobramycin patients felt that their disease was better or unchanged as opposed to the placebo group.

Next slide?

And then, this is that last slide that I made a comment on during the questions. This is the data for 36 patients who were on TOBI and 34 patients who were on placebo, who continued on through, finishing trials 002 or 003 and were enrolled in the open label follow-on study.

So here, at this point, those patients who were on placebo down over here converted to using tobramycin on the open label study. And what you see is that the tobramycin patients at least seemed to continue on with their effect. And, again, this is a small number of patients. It's not representing the total. And the patients who were placebo did seem to have a rise up in terms of their baseline FEV to match that which was seen in the tobramycin group.

Next slide?

So that's it for my presentation. I just wanted to thank several people who were involved in

the review of the study overall, and especially Tom Hammerstrom, who worked tirelessly in the statistical portion of the presentation; Beth Duvall-Miller, the project manager for this drug; the other medical officers that are involved, Marianne Mann, who is going to give the safety data now, and Alex Rakowsky, who was involved with the company in talks prior to the submission of the NDA, because his work and the work of many others at the FDA on the pre-submission made my job a lot easier.

So now I'd like to have Marianne Mann come up and give the safety analysis.

DR. MANN: Hi. It's very gratifying, actually, for me to be up here presenting the safety review of this particular application. And I say that because it wasn't very long ago that I was a clinical pulmonologist running a pulmonary rehab center and taking care of a lot of patients with cystic fibrosis, actually. So it has been a very good experience for me in that way.

It is also very challenging for me to be presenting to you today, because I realized just a little while ago that I'm the last speaker on the last day of a three-day long Advisory Committee panel meeting. So --

(Laughter.)

-- for that reason, I am challenged.

Can we go to the next slide?

I am also challenged because as a pulmonologist, I am going to be speaking to you about two topics which are a bit foreign to me -- number 1, ototoxicity, or more specifically the cochlear toxicity; and, number 2, the upward shifts in MIC that were noted for the Pseudomonas aeruginosa isolates. But I do plan on doing my very best to give an overview of these two topics.

Despite the fact that we have really had aminoglycosides available in our therapeutic regimens for almost half a century now, we don't really understand the pathophysiologic mechanism of aminoglycoside-induced ototoxicity all that well. We definitely know that there is loss of cochlear hair cells. That much is clear. But whether this is a direct effect of the aminoglycoside itself, or whether it is more of a toxic metabolite possibly that is causing the toxicity, is currently being debated in the literature.

This toxic metabolite theory has sort of come out in the literature more recently, and I think that in part it is because the scientists are noticing

that in both clinical trials and in preclinical trials aminoglycoside-induced ototoxicity is often this sort of delayed phenomenon. It is not something that occurs right away.

And, in fact, in animal studies, if they take the hair cells and like drench them in aminoglycosides, just cover them with it, you don't immediately see the toxicity. It occurs as a delayed phenomenon. In fact, clinically, we know that it can occur after therapy has been withdrawn, and months after therapy has been withdrawn sometimes.

It is also important to note that this toxicity has happened with not just the IV administrative routes of the aminoglycosides. Oral, pleural, and peritoneal installations of aminoglycosides have all resulted in cases of ototoxicity, so that is also important to note. It's not simply IV that causes it.

Hearing losses are typically noted at frequencies of 8,000 Hertz or above in the beginning, and this is important because traditional audiometric evaluations, when they are performed, usually go to about 6,000 or 8,000 Hertz and don't go any higher. So if you really want to do a very, very sensitive study -- and some studies that have been done with

aminoglycosides have looked, in a very careful way, at this. They look at 10,000 to 20,000 Hertz when they really, really want to pick it out.

Now, clinically significant hearing loss, though, is usually at these lower frequencies. So when you talk about clinically significant, or the patient is going to be actually having symptoms of deafness, this is a very reasonable cutoff to use.

The final point I'd like to make is that the toxicity due to aminoglycosides is often initially unilateral. It is not always bilateral, and that's important because I think traditionally we think since this is a systemic kind of toxicity, it should affect both ears. But often times in the beginning it can be unilateral.

Next slide?

So what are some risk factors for the aminoglycoside-induced ototoxicity? Well, number 1 would be duration of therapy lasting longer than 10 days. Prior aminoglycoside exposure also is a risk factor. Even patients who have received aminoglycosides as much as a year or more ago are at enhanced risk for this ototoxicity with each subsequent aminoglycoside administration.

Severe underlying illness, decreased

hearing at baseline, and elevated peak and trough serum levels, as we all know, are risk factors for ototoxicity.

In the study of the cystic fibrosis patients, these first three -- duration, prior exposure, and severe underlying illness -- I think are all potential risk factors.

So how was ototoxicity evaluated during these clinical trials? Number 1, patients were monitored for basically the symptoms of hearing loss. If they complained that they couldn't hear very well in either ear, that was recorded, and we have a tally of those results.

Number 2, audiometric evaluations were performed. Now, these were performed in 302 of the over 500 patients that were enrolled in the trial. The reason additional testing wasn't done in the last 200 patients is that certain study sites just didn't have the capability to do the audiometric evaluations. So we have data on 302 people. That data is, by the way, balanced between TOBI and placebo patients.

And, finally, we have the symptoms of tinnitus, which you heard a little bit about earlier, and we're going to go over a little bit more data on that.

Regarding hearing loss, four TOBI patients and three placebo patients complained of hearing loss during the study. And a little bit more about the four TOBI patients. Their hearing loss was only mild to moderate; it wasn't severe. Audiometric testing was done in three of these four patients and did not reveal any evidence of hearing loss.

Alternative causes, in fact, were present in two patients. One patient had otitis media, and as that was treated his hearing loss got better. The second patient had attended a rock concert -- another cause of hearing loss. And, importantly, all four patients had normal hearing by the end of the trial.

So at least regarding this hearing loss, there is no sign of any danger or any red flags that are going up.

What about audiometric evaluations? You heard this definition this morning. The sponsor's definition was that of a bilateral, high frequency hearing loss of 15 decibels or more at two consecutive frequencies. And using this particular criteria, which is a reasonable criteria -- this is often used to define hearing loss clinically -- no patients met this criteria, neither placebo or TOBI.

But the FDA kind of felt, look, we're

looking at this as a safety issue. We want to be very, very sensitive and try to pick up any indicators of a problem. And, again, this bilaterity, because early, early ototoxicity due to aminoglycosides is often unilateral, we wanted to sort of change the definition a little bit.

Therefore, we asked the sponsor to reevaluate their audiometric evaluations using slightly more sensitive criteria as follows: a 10-decibel hearing loss in at least three frequencies in either ear, or a 15-decibel hearing loss in at least two frequencies in either ear, or a 20-decibel hearing loss at any frequency in either ear.

Using this more sensitive, kind of graded definition, six TOBI and 10 placebo patients met these more sensitive criteria. Again, no major red flags going up here in terms of a concern for ototoxicity.

What about the tinnitus? I think tinnitus is a very important symptom to look at, because it is often the initial symptomatic manifestation of cochlear toxicity. It is high pitched, continuous, and it reflects cochlear hair damage in the basilar turn. This basilar turn is exactly where the aminoglycoside toxicity initially occurs. So this particular symptom should not be downplayed in any

way. I think we should really look at it very carefully.

Again, as you heard this morning, eight TOBI patients had 16 episodes of tinnitus, and no placebo patients had any tinnitus. These eight patients -- a little bit more information about them -- six were female, two were male, and as you heard the age was above 18 for seven out of the eight, and then there was one 15-year old patient.

Both bilateral and unilateral tinnitus had occurred with about equal frequency. About half of the patients complained of tinnitus in one ear, and the other half in two ears.

As they pointed out this morning, most of the tinnitus episodes occurred in the first cycle or the second cycle of TOBI therapy, and a few episodes occurred during the third cycle. So there was no relation.

Even though I made the point about this long duration of exposure to TOBI being a major risk factor, in this particular study of six months of TOBI therapy there was no relation to the cycle of therapy regarding when tinnitus occurred. But it is somewhat notable that 12 of the 16 episodes began while the patient was on the TOBI treatment rather than off.

What was the severity like? Well, it was moderate in three patients and mild in five. So, again, not a lot of real bad cases of tinnitus. And the duration was relatively short -- less than a week for 13 out of the 16 episodes.

One patient, however, had an episode that lasted 10 days, and one other patient had two episodes lasting 22 and 40 days, respectively.

Serum tobramycin levels were less than two microgram per ml, as you heard this morning. And, in fact, they exceeded one microgram per ml in only two subjects. But it's important because these were not obtained at the time of the tinnitus event. They were obtained routinely at, you know, preordained times throughout the study.

Audiometric evaluations -- again, not done at the time of the tinnitus, but nonetheless done -- did not reveal hearing loss. Two patients were taking ibuprofen daily as a potential confounding medicine, and two patients were receiving concurrent IV tobramycin as a possible confounding medicine.

Next?

In summary, therefore, the FDA's safety concerns regarding ototoxicity are as follows. There are really no signs of ototoxicity regarding hearing

loss or by standard audiograms which went to 8,000 Hertz. But eight TOBI patients, nonetheless, had 16 episodes of tinnitus, and we didn't see this in the placebo arm.

And we are concerned about this finding because tinnitus may be one of the earliest manifestations of aminoglycoside-induced cochlear toxicity. This leads to our concern -- what effects might longer term TOBI therapy have on cochlear function?

Moving on to the second topic, what about the upward shifts in MIC that occurred for the Pseudomonas aeruginosa isolates in the study? Basically, the analyses I'm going to be showing you are comparisons between the two arms.

The primary FDA analysis began with looking at shifts in MIC from baseline or visit 3 to visit 10 and 11. Patients with valid MIC data at visits 3, 10, and 11 were included in this analysis. And we looked at the same group of patients at visits 3, 10, and 11, and in order to get that consistent group of patients, we had 218 TOBIs and 220 placebo patients.

I'd like to make one point. You see the word "valid" up here. You may be wondering, why does

she have the word "valid"? That is because there was, actually, a quality control problem for MIC data detected in the central laboratory which did all of the MIC data in this study.

As a result of this quality control problem, the sponsor agreed with the FDA recommendation that they go back and retest visit 3, visit 10, and visit 11 data for MICs using good quality control on isolates that had been frozen. Therefore, I'm just pointing out the fact that original MIC data, if it occurred at the time of this quality control problem, are not included in any analysis. We only used the repeat data at visits 3, 10, and 11, if that's what was necessary.

The next point I'd like to make is that we recorded the maximum MIC at each visit for each patient. Now, this is important because as Dr. Montgomery pointed out this morning, there are multiple morphotypes of Pseudomonas aeruginosa for each patient. A patient could submit a specimen at visit 3, for example, with four or even five different Pseudomonas isolates.

In those Pseudomonas isolates, you might have MICs ranging from .25 up to 32. What we did in order to sort of be consistent was we just picked each

patient's maximum MIC isolate at each visit and recorded the MIC value for that patient.

We looked at shifts from baseline to visit 10, and from baseline to visit 11, for each patient. If the patient started off, therefore, with an isolate that had .25 as its maximum MIC, and by the end of the study had one as their maximum MIC, this would be considered a fourfold increase in MIC.

We looked at analyses, then, that compared the relative percent of patients in each arm with fourfold and eightfold rises in MICs. The patients in this fourfold rise, therefore, include people who went from .25 to one. Also, this includes people that went from four all the way up to 16. It's kind of a generalized group.

I'm not totally sure that .25 to one isn't also possibly a concern. It's probably not as concerning clinically to you in terms of immediate need for concern, but in terms of background shifts I still think it's important to look at this. And then to be a little bit more sensitive, we looked at those people who had eightfold rises in MIC. So now you're actually requiring them to go from .25 -- at least bring it back up to four.

All right. Next slide?

So what were the results? From baseline to visit 10, there were 33.5 percent of TOBI patients who had a fourfold rise in MIC titer, compared to 20 percent of placebo patients. And here, 22 percent versus 10 percent for this eightfold rise. Both of these are statistically significant with highly significant P values.

Move out baseline to visit 11. Same types of shifts are generally seen -- again, statistically significant that more TOBI patients than the placebo patients are having fourfold and eightfold rises in MIC titer from baseline to visit 11.

I think somebody earlier asked about changes in MIC from visit 10 to visit 11, trying to get a sense of is there any kind of transient effect that is dropping off over time. And it looks like, looking at the isolates with fourfold rises, there is certainly a dropoff in the TOBI patients here from 33-1/2 percent down to 26 percent. So there may be perhaps some transients.

But what is notable is that the same dropoff -- 20 down to 14 -- the same like six percent dropoff is seen in the placebo arm between visit 10 and visit 11. So I'm not sure if this is really transient increases in MIC or if it's just an overall

reflection of the variability in the lab, the variability in the patients. Who knows?

Next?

How about eightfold? Again, you see a dropoff from 22 down to 17 percent, and from 10, in the placebo arm, down to four percent. So you do see this similar kind of dropoff in this analysis, but it's a very similar dropoff between TOBI patients and placebo patients.

The second sort of major way the FDA decided to look at the data was we tried to look at the shifts in MIC from baseline to final MIC for each patient. Now, this didn't require a patient to have visit 10 and visit 11, the MIC data. It actually included people who had any valid baseline MIC data and any valid MIC data that occurred after visit 5. Visit 5 was chosen because that's the visit right after the first cycle of study drug therapy. So at least patients were exposed to 28 days of study drug.

And we had 250 TOBI patients, of the 258 that were enrolled. So it's very inclusive. We had 246 placebo patients, of the 262 who were enrolled. So that was fairly inclusive.

Again, we recorded the maximum MIC at baseline and at the last valid MIC that we could find

for the person. And we looked at shifts from baseline to last MIC. And, again, we looked at the fourfold and eightfold rises in MIC titer.

Next slide?

Before I actually get to the results, however, I think it's nice to sort of look at what was the last visit that contributed this MIC data. Was it really balanced between treatment arms? And the answer is, clearly, yes.

We have the majority of the MIC values here coming from visit 11, which is what we'd expect. That was the last visit in the parallel study. It's where we have most of our data for both placebo and TOBI. We have a few patients here who went into the open label portion of the trial, so we have some longer followup in this group.

We have a few people who stopped the study at visit 10. We couldn't find anything beyond visit 10. And then we have a few people who withdrew from the study perhaps early, and yet had a valid MIC data point, and we included them in this analysis, because I think it's important to look at people who withdraw and do an inclusive analysis including them.

And this data -- it's not going to look very different from the visit 3 to visit 11 data,

since most of this data comes from visit 11. But it, again, shows a statistically significant greater percentage of TOBI than placebo patients having fourfold and even eightfold rises in their MIC titer.

Okay. As we've presented all of these shifts, I know you're probably still thinking .125 to two, and two all the way up to 64 are sort of different to me in my mind. And I'd like to just know, what is the relative percent of patients who had MIC values above eight at baseline, visit 10, and visit 11, for each treatment arm? So we did this analysis as well.

Again, we used that same database of the 218 TOBI and 220 placebo patients who had visit 3, visit 10, and visit 11 data, so we could look at the same group of patients over time.

You can see at baseline there are slightly more TOBI patients than placebo patients who have these what are traditionally actually thought of resistant, if you're talking about intravenous tobramycin or parenteral tobramycin therapy. These would be called resistant isolates. So, in that sense, the TOBI arm is at a slight disadvantage at baseline because 14.2 versus 10.9 percent of placebos have these high isolates, high MIC isolates.

At visit 10, however, we go from 14 all the way up to 26.6, whereas here we go from 10.9 up to 17. This rise is somewhat greater, I think, than what you're seeing in the placebo arm. And it stays, at visit 11, fairly consistent. Placebo arm, on the other hand, drops to below what it was at baseline.

I think the point -- another point to be made here, I think these shifts are concerning in the TOBI arm, but you see a lot of noise. You see a lot of movement, even in the placebo arm. And what is the reason for all of this sort of movement, even in placebo patients? I think it's probably a number of things.

It might reflect the natural variation in the assay itself. The assay has a twofold variance as it is being done in terms of error, and we just may be seeing some movement in terms of the assay itself.

Secondly, we are talking about patients who are giving us sputum. And as a pulmonologist, that is something I do know a lot about. And sputum can sometimes be very good quality sputum, and sometimes it can be not so good. So you're going to get a little bit of a fluctuation over time, I think, just based on the samples you are getting from your patients.

Finally, as we pointed out this morning, a fair number of the TOBI and placebo patients in this trial received not only the study drug, but they received other aminoglycoside and other systemic antibiotic therapy, which might cause some fluctuation even in the placebo arm. Therefore, the FDA did a subset analysis in those patients who did not receive systemic anti-pseudomonal antibiotics during the study.

We could find 159 TOBI and 127 placebo patients who met this criteria of not receiving any systemic anti-pseudomonal antibiotic therapy during the six-month trial and who had either a baseline or a visit 10 or 11 maximum MIC value. And we could look at this database to see what happened in this group.

Now, I think it is important to note there's 159 TOBI patients who didn't require these antibiotics and 127 placebo patients -- again, just as an efficacy end point, something worthy of note.

In this particular subgroup of patients, however, we still see that the fourfold right and eightfold rise in MIC titer is statistically significant. I believe the P value here is about .03, and here .001. So we still see that even in patients who are not exposed to anti-pseudomonal antibiotics,

and who have no other confounding antibiotic pressures to bring out resistance, the TOBI patients are having more shifts.

And there are also -- this is the people with MICs greater than eight. Twice as many, twice the percent of TOBI compared to placebo patients had MICs greater than eight at visit 10 or 11.

Now, I've shown a lot of slides now about shifts in MIC. That is a lab phenomenon. What about the clinical data? As you heard this morning, the clinical data is actually very supportive of TOBI. The percent predicted FEV1 improved. The CFU counts decreased. But as many of you noted this morning, this effect was somewhat less remarkable as each successive cycle of TOBI was given. So it did wane a little over time.

Time to IV antibiotic use was delayed. This was shown very close, as John pointed out earlier, in one trial. I, actually, just called it both trials. It was very close in the one trial, and it was definitive in the second.

Time to hospitalization was delayed. This was shown in one of the two randomized trials. And it was also shown in the overall combined data. And as you heard, there were four deaths, and they all

occurred in the placebo arm. So looking at very basic clinical type data, no, there is no sign of any worrisome thing that clinical -- overriding clinical resistance is occurring that is causing patients to do any worse.

I think one group of patients to look at a little bit more closely, though, are the people who withdrew, because when you withdraw from a study there is always a reason why, and sometimes that reason is clearly stated. If the patient has -- if the clinician has a concern about resistance, we'd like to know about that. And sometimes it is not clearly stated, but we'd still like to know what was their MIC value at their final study visit, nonetheless.

So there were 21 placebo patients who withdrew from the study prematurely. None of the patients were withdrawn because the clinician had a concern of resistance. Four of the patients who withdrew early, though, did have MICs above eight, above or equal to eight, at the final study visit. And one of these four also had maltophilia. I'm sorry, I can never pronounce the "S." One of these four also had maltophilia present at their final study visit, and that had an MIC of 256.

Sixteen TOBI patients withdrew

prematurely. One was withdrawn because the clinician was concerned, actually, about resistant Pseudomonas aeruginosa pneumonia. Somewhat surprisingly, though, the central lab data in this person from the study didn't really reveal any resistance. I think the peak MIC was four for this particular patient. So the central lab data, obviously, didn't agree with whatever lab the clinician was using.

Six patients had Pseudomonas aeruginosa isolates with an MIC above or equal to eight at the time of their final study visit. Three had S. maltophilia, and one person had xylosoxidans with a high MIC. So I think if you count these up -- 6, 7, 8, 9, 10, 11 -- we have 11 out of 16 patients in the TOBI arm who withdrew prematurely, and in whom it is possible that some of these resistant isolates may have played a role.

Next?

What about the open label? Well, in the open label, six placebo patients went on to receive TOBI, and yet withdrew during the open label trial. Two withdrew due to the clinical emergence of resistant organisms, and one withdrew because they had increased respiratory systems, and they were noted to have an MIC for Pseudomonas aeruginosa of 128 at their

final study visit.

What about the patients on the TOBI arm who remained in TOBI for open label? Well, seven of them withdrew during the open label trial. Three were due to clinical concerns by the clinician that resistant organisms were emerging. One patient felt no better and had a final MIC for Pseudomonas aeruginosa of 32, and one person had no improvement.

This person had S. maltophilia consistently from visit 5 on, yet stayed with the study up until I think about visit 13 or 14. I can't remember for sure. But at least they had an MIC very high for S. maltophilia at the end of their visit. So here we have five out of the seven TOBI patients who withdrew prematurely, again, where resistant organisms may have played a role in these patients' decision to withdraw.

In summary, therefore, upward shifts in MIC were more marked in the TOBI arm than the placebo arm over time for the Pseudomonas aeruginosa isolates. But there is little evidence overall in the whole clinical trial that these shifts had any clinically -- you know, had any clinical relevance regarding clinical deteriorations during the six-month study.

If you look at patients who withdrew,

though, you can sometimes see that resistance may have been a contributing factor.

This leads to our last concern/question for the panel: will rises in MIC continue to occur with longer term TOBI therapy? And will this eventually have an impact on clinical outcomes?

Thank you.

I have one overhead, just to put up briefly if that's okay.

CHAIRMAN CRAIG: Sure.

DR. MANN: When I presented the data on the fold changes in MIC, I really only talked about fourfold and eightfold. So you know what happened on the upper portion of these graphs, where you can see the fold changes for MIC is on the X axis.

I wonder if this pointer will work. Well, it does, sort of.

From about here on is the data that I just presented. This area, and down here, this area.

But I think it's kind of nice to look at the entire distribution for fold changes in MIC and what percent of patient specimens fell in these different fold changes. You can see that most people are within a twofold dilution, and so there is -- it's where the sponsor said 85 percent of people really

didn't change, and that's very true.

There is a large group of patients here who stayed within one to twofold dilution of their baseline MIC. But it's this bump and this bump that we're concerned about.

Thank you.

CHAIRMAN CRAIG: Thank you.

Our next portion -- I think we can ask FDA questions after we have the open public hearing. There are two speeches there, and then we can get on with our committee discussion.

The two open public hearing speakers -- the first one is Robert Beall, President and CEO of the Cystic Fibrosis Foundation. He has five to seven minutes.

DR. BEALL: Good morning.

I appreciate the opportunity to represent the Cystic Fibrosis Foundation and the 30,000 individuals affected by this disease at this very important meeting. Let me assure you that the thoughts and the hopes of these young individuals with cystic fibrosis and their families are with the deliberative body here today.

There has been a dramatic improvement in the life expectancy of cystic fibrosis patients over

the last three decades. However, with the exception of the introduction of Pulmozyme in 1994, the treatment regimen for cystic fibrosis remains essentially the same.

We use antibiotics to treat the infections, postural drainage to remove the excess secretions, and aggressive enzyme replacement therapy to offset the pancreatic problems. These strategies have been, and for the immediate and foreseeable future will remain, the cornerstone of CF therapy.

The improvement of life expectancy over the past three decades has improved significantly, and these can be attributed to three factors. First, as Dr. FitzSimmons pointed out this morning, the network of Cystic Fibrosis Foundation accredited and supported CF care centers that deliver specialized care to this specialized population. Secondly, the availability of new antibiotics. And, thirdly, more aggressive nutritional intervention.

For the most part, physicians have been limited to improving the tools that are already available to treat cystic fibrosis. But the unfortunate fact remains that despite the increases in life expectancy, every individual born with this disease faces a premature death sentence, and each

faces a quality of life which everyone in this room would consider unacceptable.

The prospect for treating the causes of cystic fibrosis through gene therapy and other pharmacological means has never been as hopeful as it is now. Currently, there are nine clinical trials underway that are treating the root cause of cystic fibrosis -- a defective gene. Other trials are underway using drugs to correct the protein product of the defective gene.

In the meantime, as these therapies, as these ultimate therapies are being refined, fighting the chronic lung infections and the consequent inflammatory response remains of critical importance to our caregivers.

Despite our efforts to identify new antibiotics during the early '80s, with the exception of the quinolones, it became apparent that no new pipeline of new antimicrobial agents existed that could effectively treat cystic fibrosis-related infections. So we ask ourselves, can we improve upon those that were already available?

The first drug candidate was an obvious one. Intravenous aminoglycosides have probably contributed more to the improved life expectancy in

cystic fibrosis patients during the last three decades than any other antibiotic.

In addition, during the 1980s, as with many groups desperate for more effective therapies, cystic fibrosis patients and physicians began to ask the question: could aminoglycosides be administered directly into the lungs, via aerosol, in higher concentrations without seeing the consequent resulting side effects observed in traditional intravenous usage?

Convenience, rather than scientific method, dictated the dosage selected. In fact, the patients basically took what was in the intravenous vial, then added one or two of these vials to the nebulizer and went from there. Concerns regarding dose and preservatives in the preparations were not apparent in this early stage of aerosolized aerosol usage.

In 1986, the Foundation, along with Dr. Arnold Smith and Dr. Bonnie Ramsey, began to ask some questions related to the use of aerosolized antibiotics in CF patients. We asked whether or not aerosol antibiotics could really be effective. And, if so, what was the optimal dosage and the optimal delivery method.

The study designed to find these answers resulted in a publication in The New England Journal of Medicine in 1993. But these results did not get a drug to market. At that time, the Foundation went to PathoGenesis Corporation and asked them to consider taking this product to the next step. The response to that request is why we are here today.

The pace at which this drug has moved through the subsequent developmental phases has been remarkable. The formula for this incredible feat has included: 1) a network of patients who are eager, and I would say, more importantly, desperate to participate in research trials to improve their quality of life.

Secondly, the availability of cystic fibrosis care center network, comprised of dedicated groups of caregivers, who are committed to conducting and evaluating new therapies for cystic fibrosis patients.

Thirdly, a company enthusiastic to develop new products, not just blockbuster drugs, but also therapies designed for a smaller patient population like cystic fibrosis.

And, fourth, but certainly not finally, the dedicated staff at the Food and Drug

Administration. The FDA review staff has worked effectively with the private sector to evaluate and review this new drug product.

Our partnership is unique -- a private foundation, a pharmaceutical company, and a regulatory agency -- all working together to promptly evaluate new products. We hope that this cooperative effort will continue to strengthen and will serve as a model to expedite future developments in cystic fibrosis research.

You, the members of this panel and staff, have sorted through reams and reams of paper documenting FEV1s, antibiotic usage, hospitalization rates, etcetera. I believe that one of the most significant outcomes of this study may be found in some of the less-than-objective data. It has been reported, and is a fact, that patients say they feel better.

To feel better is something that individuals with cystic fibrosis dream about -- to be able -- to struggle not to have to take a breath, to be able to walk up a flight of stairs, to run down a soccer field without having to stop halfway. These are simple things to you and me. We take them for granted. But for an individual with cystic fibrosis,

it can change their life from one of hopelessness and despair to one of hope and optimism.

In addition, many of these patients, as a result of aerosol delivery usage, have been able to prevent from having to go to the time-consuming cleanouts, as they are often called to do, and that frequently force them to miss school and to miss work. The convenience of aerosol has clearly made a difference in not only how they feel, but in allowing them to resume the efforts and education, career development, and raising families.

Not only are the patients excited about TOBI, but physicians are excited about having a new therapy to approach treating this disease. We already know that over a third of our patients use aerosolized antibiotics. This was from data reported in 1995. The results from the Phase III study indicate that TOBI could be applicable to thousands of patients who have already been diagnosed with cystic fibrosis.

The availability of such an innovative and well-studied drug may unlock the handcuffs that have frustrated our caregivers for decades. They finally will have a new tool that may reduce morbidity and possibly the mortality, while providing a better quality of life for the patients with cystic fibrosis.

In addition, we are already applying the same rigorous process that we applied to the development TOBI to explore other aerosolized antibiotics.

Today, the entire scientific community and CF community is anxiously watching the landmark experiments in gene therapy for cystic fibrosis, the route to cure cystic fibrosis. While everyone awaits the results of these studies, TOBI must be made available now. We need it to treat the young individuals with cystic fibrosis, so they can better manage their disease until we achieve the ultimate cure. Clearly, TOBI will become a major weapon in our fight to control the progressive lung destruction of this disease.

The deliberations that are about to take place over the next few hours will profoundly impact on the lives of individuals with cystic fibrosis. We appreciate the opportunity to represent them. We also appreciate the dedication of the scientists, the CF care physicians, the FDA staff, and the hundreds of patients who have participated in these extensive studies.

We look forward to the day when we can reflect back on this meeting and identify it as truly

historical. It will represent an important milestone in the long, sometimes treacherous, and frequently painful trail that we have followed to have to accomplish our ultimate goal -- a cure for cystic fibrosis.

Thank you.

CHAIRMAN CRAIG: Thank you, Dr. Beall, and also, thank you for the work of your foundation.

Are there any questions from members here?

Fine. The next speaker will be Preston W. Campbell, III, Director of the Cystic Fibrosis Foundation Care Center, Vanderbilt University Medical Center.

MR. CAMPBELL: Good morning.

I also would like to thank the committee for an opportunity to speak today. My name is Preston Campbell. I'm a pediatric pulmonologist. I also had the opportunity to co-chair the Cystic Fibrosis Foundation's Center Care Committee, which oversees the 113 centers that Dr. FitzSimmons told you about. I am also the Director of the Vanderbilt CF Center located in Nashville, Tennessee.

I would like to make a few comments about the current use of aerosolized antibiotics, and update you on a recent consensus conference on aerosolized

antibiotic use in cystic fibrosis, which was sponsored by the CF Foundation.

The cornerstones of CF care are antibiotics for lung infections, therapies to remove thick mucus from the lungs, and pancreatic enzymes to enable growth. The improvement in aggressive implementation of these therapies have been associated with a significant improvement in survival, but this impressive improvement in survival simply isn't good enough. Every year too many wonderful young people die of this disease for any of us to be satisfied.

Now, the battleground for future advances in CF survival is within the CF airway. In order to prevent or delay the development of life-threatening lung disease, CF researchers and clinicians have developed a two-pronged attack. A major offensive, as Dr. Beall has told you about, has been directed at curing CF by correcting the basic defect.

Now, while we wait for this to become a reality, the second offensive is aimed at improving routine therapies for the lung, such as antibiotic therapies. Antibiotics were initially given orally or intravenously, but the limitations of oral and intravenous antibiotics resulted in caregivers delivering the antibiotic directly to the lung by

inhalation.

By the early 1980s, there were a series of clinical trials that began to report variable success in using aerosolized antibiotics. I first used aerosolized antibiotics in a patient with moderate severe lung disease who I could not keep out of the hospital. The success in that patient led to more widespread use among our patients.

I suspect such anecdotal experience by an increasing number of CF doctors has played a dominant role in determining the current use of aerosolized antibiotics in CF patients. Aerosolized antibiotics are now routinely used in cystic fibrosis patients across the country. Surveys in the last several years have shown that almost all U.S. CF physicians used aerosolized antibiotics. Approximately 30 to 40 percent of CF patients are on chronic aerosolized antibiotic therapy. However, there is great variability in their use.

For example, different drugs and doses are used, and the indications for using them vary from doctor to doctor. Tobramycin is the most frequently used antibiotic, but other antibiotics, such as gentamicin and colymycin, are also used. And while they are mainly given as maintenance therapy to

suppress Pseudomonas aeruginosa, they are also used alone or with parenteral antibiotics to treat pulmonary exacerbations.

In an attempt to better understand the appropriate role for aerosolized antibiotics in cystic fibrosis, including drugs under investigation, the Cystic Fibrosis Foundation convened a consensus conference for the use of aerosolized antibiotics in cystic fibrosis. It was chaired by myself and Dr. Lisa Samen, a pediatric infectious disease specialist at Columbia University, and a recognized expert on lung infections in cystic fibrosis.

The consensus committee was convened in late September and consisted of approximately 25 participants from the United States, Canada, and England. For two days we met and reviewed all of the available data regarding the safety and efficacy of inhaled antibiotics in cystic fibrosis patients.

Investigators from PathoGenesis were invited to present the data from the Phase III trials with preservative-free, 300-milligram tobramycin.

Although the consensus document is still in draft form, I'd like to make three points based on the progress made to date. First, only aerosolized, preservative-free tobramycin has been studied in a

fashion allowing evidence-based assessment of clinical and bacteriological effectiveness. Both the FDA and PathoGenesis are to be applauded for the scientific rigor in which preservative-free tobramycin has been developed and tested.

The process is now considered to be the paradigm for the development of future aerosolized antibiotics for cystic fibrosis patients. Not only were we able to evaluate the risk-benefit ratio of this drug, but we have a much more thorough understanding of the aerosol therapy in general.

Second, our consensus conference determined that aerosolized, preservative-free tobramycin at a dose of 300 milligrams twice a day, given every other month, is effective. CF patients aged six years and older who were colonized with Pseudomonas aeruginosa, and had mild to moderate lung disease, experienced improved pulmonary functions, decreased hospitalizations, and a reduction in Pseudomonas aeruginosa sputum density in those Phase III trials.

These results are not only statistically but also clinically significant improvements. For example, patients may feel better with a 12 percent improvement in the FEV1, and avoiding disruptive and

expensive admissions means the world to them. In addition, they are practical. Our patients' pulmonary functions are checked regularly and are considered sensitive measures of improvement or decline by CF caregivers.

Finally, 300-milligram tobramycin appears to be safe. The clinical and microbiologic risks were acceptable to the panel. They realize that risk occurring only after years of use may not be observed in a six-month trial. Therefore, recommendations were made to continue to monitor the clinical toxicity and the potential selection of a resistant bacteria.

These recommendations can be incorporated into CF practice guidelines. These are guidelines that every CF center and every caregiver has throughout the network.

In summary, aerosolized antibiotics have emerged as standard therapy because effective long-term suppression of Pseudomonas in the airway is needed. However, current practice patterns are variable and the risk-benefit ratio of currently used drugs is unknown. Only aerosolized, preservative-free tobramycin has undergone adequate pharmacologic and safety testing.

Clinical trials for this drug have

demonstrated it to be safe and effective and have enabled us to make recommendations for its use. If approved, I believe it will justifiably replace other antibiotics as the preferred aerosolized antibiotic for cystic fibrosis patients.

Thank you.

CHAIRMAN CRAIG: Thank you very much.

Any questions from anyone?

Okay. Now let's move on to the committee discussion. But, specifically, let's give some time for any questions that anybody has for the FDA presentation.

I guess I would ask one on the MICs. Could you see any -- did you look at all to see if there were 16-fold increases? And the reason I ask that is many years ago we worked with trying to look at these permeability mutants and had great difficulty sometimes getting MIC -- we'd get an occasional one up to maybe 16-fold, but we could never get them beyond 32 for tobramycin.

DR. MANN: This data that you asked about is in this overhead that I am showing here where MICs of fourfold increase are shown here -- eight, 16, 32, and 64. So you can see that it's not just fourfold. A lot of people are at eightfold; a fair number at 16;

32, the curves hit one another; and then, 64 or more fold increases are shown at the end. This, by the way, is visit 3 to visit 10 changes.

From visit 3 to visit 11, again, the same kind of display. It's there at fourfold -- it's really not there at fourfold. It's there at eightfold, 16, 32, and 64, from visit 3 to visit 11.

So when I present the data of eightfold or more, it's not just eightfold. It's 16, 32, 64; it keeps -- it's consistent.

CHAIRMAN CRAIG: The other question that I guess one always has is, you've just been picking the organism with the highest MIC. Is there any evidence or any data that you have that would give you an idea of what percentage of the population of total organisms does that organism represent?

DR. MANN: For that, I could refer, I think, to the sponsor. They have distributions of MICs for all 800 isolates in the study. And when they show those curves -- I think they might have shown them this morning. I'm not sure. But when they show those curves, there is a slight blip out at eight, 16, 32, 64. There is more TOBI patients having those isolates.

But I don't have that data for fold

change. I don't --

CHAIRMAN CRAIG: No. What I'm talking about is trying to look at a population analysis and an individual patient's sputum. In other words, what percentage of the organisms that are in that sputum are organisms that have the very high MICs? Is it represented as one out of 100, or is it 99 percent of the organisms that have the high MIC?

DR. MANN: Yes.

CHAIRMAN CRAIG: Because if it's --

DR. MANN: I see --

CHAIRMAN CRAIG: -- a relatively small percentage, it could still explain why one is getting a good effect from the drug, and --

DR. MANN: Right.

CHAIRMAN CRAIG: -- even though it looks like we have some resistant organisms around.

DR. MANN: Right. No. You're absolutely right. And I don't have exactly that data to show you, but --

CHAIRMAN CRAIG: Okay.

DR. MANN: -- you're right.

CHAIRMAN CRAIG: Does the sponsor have --

DR. MANN: That would be very good.

DR. MONTGOMERY: Could I have Slide M12,

please? I don't know which screen you're going to go on. Hopefully, it --

What I'm going to show here is curves on percent of isolates, and then having two curves. The highest density isolates -- we did do quantitative cultures, which allow us to tell what the highest density is, and what the highest MIC isolates are, and the percent of isolates, showing that the highest density isolates tend to have lower MICs than the highest MIC isolate. There's more dense -- I take that back.

The highest density Pseudomonas aeruginosa isolates have lower MICs, on average, than the highest MIC isolates. And so this is at baseline, so that the high MIC isolates aren't overrun.

Now, the question is: what happens at the end of therapy? Do you switch the curves?

And could I have the next slide, please?

And here, the curves are -- the curves sort of show the same thing -- the highest density and the highest MIC. And so you still haven't seen the switch.

The exact percentage -- the highest MIC is equal to the highest density in 50 percent of the patients at baseline. At week 24, it goes to 53

percent. So this relationship just seems to be preserved, even in the face of TOBI therapy.

CHAIRMAN CRAIG: It's sort of a little bit of what I'm looking for but not entirely. Obviously, I think the only way that you gave the information I'm looking at is if you did population analyses on the sputum, and how you would do that would be plating the sputum on antibiotic-containing plates with increasing concentrations of the drug, so that you can actually see, then, among the population what percentage of the organism are susceptible at different MICs.

I think that's really the only way that you can really get that kind of data to see where the distribution of resistant organisms is among the total population of organisms. And I assume you don't have any data like that. No.

Any other questions of the FDA? People are getting hungry.

(Laughter.)

So I guess we should go on to talking about -- Dr. Melish?

DR. MELISH: I had some questions about adverse event data. Were patients specifically asked questions at each visit about things that are odd, like voice alteration? Or was this something that was

volunteered?

DR. MANN: I believe the sponsor might be able to answer that question.

DR. QUAN: Our adverse event data, for the most part, represent unsolicited adverse experiences. There were some visits at which a questionnaire regarding pulmonary exacerbations was included, but that was not every visit.

DR. MELISH: So I'd like to know a little more about voice alteration. Is this in some way -- you mentioned you thought it might have to do with effects of the aerosol medication itself on the vocal cords.

DR. QUAN: Yes.

DR. MELISH: But it's also possible it could have a relationship to hearing at that time, or tinnitus. What was it that they were saying, that they couldn't sing, their voice was hoarse, they --

DR. QUAN: What was reported --

DR. MELISH: -- spoke too loud --

DR. QUAN: Yes. What was reported most often was hoarseness, and it was most often mild. A few patients reported moderate voice alteration. It was limited in duration, and it resolved.

Does that answer your question, or --

DR. MELISH: Yes, it does. It's just, you know, it did fall out as even more important among the cases than tinnitus, and it is such an odd symptom that I -- you know, I was also interested that you said that it occurred in cystic fibrosis patients when they were taking the enzyme aerosols.

DR. QUAN: Yes. It is actually reported in the DNase trials that voice alteration was more common in the treatment group. And since most of the patients that were in our study were also taking DNase, that, you know, may have contributed as well.

DR. MELISH: Thank you.

CHAIRMAN CRAIG: Dr. Azimi?

DR. AZIMI: In measuring the MIC of the tobramycin for the isolates, as we all know, these isolates of Pseudomonas are highly mucoid. And you said you used sensititer, the microdilution. Did you have any problem reading your MICs with that? Was the diffusion method not a better method to measure the MICs for these isolates?

DR. PITLICK: I think Jill Van Dalfsen will answer that.

MS. VAN DALFSEN: Well, as you know, I don't think there is a great system yet for testing mucoid CF isolates. I know there is ongoing work with

some of the researchers in the CF Foundation to try to address that question and come up with the best method.

We feel that because they manually read these after an 18- to 24-hour incubation that helped to minimize some of the problems associated with mucoid isolates -- in particular, in the rapid automated systems that have been widely noted. And so I do know that if they had patterns that looked unusual, they always repeated those a second time to try to confirm that isolate's MIC.

CHAIRMAN CRAIG: Yes, Dr. Henry?

DR. HENRY: Well, I think the data that has been shown just prior to this, that the higher density colony count or the higher densities still had lower MICs, that you saw this shift to high MICs with lower densities.

But I guess the question that is still in my mind that I think is probably there but I'm not being able to put it together right -- and that is, were there patients who had multiple strains of Pseudomonas aeruginosa with varying antibiotic profiles, and tobramycin MIC specifically, that you weeded out the susceptible population, and that in certain patients they were left with a single

population at a higher MIC?

And you always worry that you're going to kill off the sensitive ones, and then what you're left with is a patient heavily colonized with something that is harder to get rid of.

DR. GARBER: We've taken this on at a research level again, and that means taking all of the different morphotype isolates at each of the different visits and trying to follow through, and we've done genotypic analysis with PCR fingerprinting approaches, and so forth, to try and get a feeling for this.

And I guess what I can tell you is that all of the different patterns that you might expect showed up. There were cases in which after treatment the dominant organism because a resistant species. But, in fact, that wasn't the most frequent. It was very often that the -- that a sensitive strain was the highest CFU, the highest density organism, and that the high MIC one trailed below that by, you know, a good log.

And then, there were all of the things in between in which it's not particularly related to drug treatment. There was variation. And so we're talking about a population of microbes in the lung which are changing.

I mean, one of the interesting things about this whole treatment thing is we're going from essentially not a lot of aerosol antibiotic treatment to a six-month dosing, and we're watching that population shift and I don't think we can extrapolate easily to where it's going to go, because this is the first time we've watched in this much detail these events.

And then, I think all of the -- there is lots of noise in between. It's very difficult, and we have obviously looked for patterns and not been able to come up with good ones.

Does that give you a little bit more of a feel? It's a complex microbiology.

CHAIRMAN CRAIG: Clearly, one of the things that we found many years ago when we did our studies with these mutants is that they were clearly much less virulent in animal models.

Alice Prince, have these -- do you know if these more resistant organisms have been looked at for the kind of substances that are produced and things that are associated with problems in cystic fibrosis?

DR. PRINCE: In fact, the isolates you get from the older patients that are chronically colonized have lots of the alginate formation. Those, in fact,

are down regulated for many of their virulence factors and they are somewhat less virulent.

CHAIRMAN CRAIG: So even for --

DR. PRINCE: It's very hard to do the studies unless you have isogeneic strains that you can --

CHAIRMAN CRAIG: Right.

DR. PRINCE: -- compare in a model.

CHAIRMAN CRAIG: Right.

DR. PRINCE: But, in general, that's true.

CHAIRMAN CRAIG: Okay.

Yes, Dr. Danner?

DR. DANNER: I'm not sure I got this correctly. But there is no data on distribution of the drug in the lung, is that correct, or is there data on that, in terms of --

DR. PITLICK: That's correct. The black box that Dr. Alexander showed is appropriate. We actually have some data on -- radiographic data on the distribution of tobramycin in lungs based on particle size, and I'd ask Dr. Montgomery to illustrate that -- the distribution of various particle sizes that are in the lung.

DR. MONTGOMERY: It's very difficult to sample. Even if you sample for available odds, you

don't really know if you're getting approximately or whether you're distantly away.

It is known, though, that particle size is a major determinant of deposition. I can at least illustrate what that does for the different particle sizes, if you're interested.

DR. DANNER: Hasn't this been looked at, though, with radio-labeled drug for other things in --

DR. MONTGOMERY: I will show you such slides.

Could you give me Slides L2, 3, and 4, please? 1? Okay. This is not a cystic fibrosis patient. In fact, this is yours truly glowing in the dark with a gamma counter with -- breathing technetium DPTA in studies I did in the mid '80s when I was developing a drug called aerosolized pentamidine, trying to figure out what particle size to use.

And this was a -- this is a one micron particle size, and, as you can see, it's a posterior view. And, as you can see, here are the lungs. The lungs are well illustrated.

In the sitting position, though, as you can see, there is less deposition in the apices. Most of your ventilation actually goes to where your profusion is, and so this has been a problem, at least

in aerosol pentamidine. And it's one of the reasons why even though you have a sputum concentration, it may not be reflective of the concentration in various parts of the lungs.

Let's go on to the next slide, please.

This is a slide of five microns, and what has happened here is that there has been a lot of oral pharyngeal deposition, again, in a posterior view, and I've swallowed it. And, therefore, my stomach is glowing in the dark. And these are studies I can't do anymore, because I'm in industry.

But the -- and you can see the major airways are outlined very nicely, but you don't get any peripheral airway deposition.

And the third slide, please, is -- this is three, and this is what we chose as the median size. But I think the problem is is that if you breathe an aerosol, you are going to have less deposition in the apices, and so there is a lot of variability inside the lung. And that's maybe one reason why our doses are important to be in excess of 10, actually, MICs, because you're not going to get the same amount in one part or the other.

DR. DANNER: I'm thinking more of the data that the FDA showed suggesting that there was perhaps

a better effect in patients with higher FEV1s. And does good distribution in the lung vary based on lung function?

DR. MONTGOMERY: Well, we've shown similar data with the FEV1 treatment effects. And since your -- we can discuss all day the difference between absolute and relative change, but if you have a relative change with a high baseline, it's more of a larger absolute change. We've shown the same.

So you probably are getting more -- you're probably getting a little better breathing. But in spitting up the sputum concentrations by FEV category, or by age, which sort of controls for lung severity, because usually the older patients are the sicker patients, we saw no difference in sputum concentration levels, or between males and females, which have different anatomy, too.

So I think there is so much variability between each patient and each patient's disease it's very difficult to tailor therapy for an individual patient or for an individual patient group.

DR. DANNER: Thanks.

But there is no data on distribution of the drug in the lung based on patient lung function?

DR. ALEXANDER: If I could make a comment

here. I did try and look for data that spoke to that, and basically there is very limited studies at all of distributions of aerosol in cystic fibrosis patients at all. And so that is a concern, and that's one of the reasons that I pointed this out.

In terms of the sputum concentrations and the lung function, again, we saw the same thing that Dr. Montgomery had mentioned -- that when we tried to look with correlation coefficients to try and correlate the sputum concentrations to things like difference in FEV, difference in FVC, changes in CFUs, we just found very low correlation coefficients. And so the variability, for other reasons, is much greater.

So we don't have any information with this drug related to its distribution inside of the lung, and we have precious little data in the literature to talk about distributions of aerosols at all in cystic fibrosis patients.

DR. MONTGOMERY: In addition, we have precious little techniques to do those studies, because if we had we probably would have done them. They're very interesting to us, but there's just not the methodology developed yet to do that.

CHAIRMAN CRAIG: Okay. Any other

discussion/comments?

DR. PITLICK: Dr. Craig?

CHAIRMAN CRAIG: Yes?

DR. PITLICK: If I may correct a previous statement. We talked about sputum concentrations in the lung at six hours. Those levels are, in fact, 10 percent of the peak levels. So --

CHAIRMAN CRAIG: It's still 100 --

DR. PITLICK: -- more in some cases. At 10 percent of 1,200, it is still 120 microns per gram.

CHAIRMAN CRAIG: Okay. Well, let's start with the questions, then.

The first question is: do the safety and efficacy data presented support the approval of TOBI for the management of cystic fibrosis patients infected with Pseudomonas aeruginosa?

And in answering that question, I think one of the things that we also need to look at it is, does the six-month data support the use for chronic therapy, since that is what they're going to be planning. We did see a little bit of additional data, more limited number. But at least from what I saw, it looked like the -- that the improvement was still there in FEV1, and that there was also, in the group that was crossed over, there was an increase in the

FEV1.

Any one of the members want to comment at all on the question of whether do they think the six-month data really is sufficient for chronic use of the drug?

Carl?

(Laughter.)

You're going to leave pretty soon, so I'm going to force you to say something before you leave.

(Laughter.)

DR. NORDEN: I don't know. But my instinct, which is never very -- you know, a very good scientific measure, would say yes. And I think that the data that I've seen certainly support the use for a six-month period. And I think that, clearly, 1A is going to be that there is additional -- the additional information that is necessary is going to be to continue to accumulate data after six months.

But I would be comfortable, at this point, I think, with the data that we have to approve it for an indication for longer use, with the understanding that if the data shows that it -- the effect wanes and it's no longer effective, that the indication has to be changed.

CHAIRMAN CRAIG: Dr. Melish?

DR. MELISH: Well, I would agree. I think that we have a -- that there is a very -- the fact that there is a network of cystic fibrosis centers with a commitment to monitoring this makes it much more likely that these answers will be gotten than in many other situations where you approve a drug on the basis of short-term information and don't know what will happen.

I think that, clearly, it is not enough to know whether this is going to be good for a year, five years, 10 years, from the information that we have, because some of the trends that we have seen, or some of the possible other things we might want to look at in the future, might indicate it could lose its effectiveness.

But since it is -- you know, since there will be almost assured followup for these questions, I feel very much more confident that this is an appropriate thing to approve.

CHAIRMAN CRAIG: Dr. Prince?

DR. PRINCE: If I could just make a comment about resistance. This is the only disease I've ever seen where people chronically have 10_8 organisms in their lungs. And what really has made a huge difference -- I don't think Stacey showed it --

is -- actually, Lisa Samen has a slide where she shows the introduction of each of the new betalactam antibiotics and survival in CF.

And so as a patient group that is dependent upon the activity of antimicrobial agents, this is the most motivated group that exists. And I was very concerned when the floraquinolones were made widely available, because we're using them in -- even though you're not supposed to, you see it widely used in little kids.

But the clinicians and the patients, just as you see the patients dropping out here, are so concerned that they're going to have resistant organisms, they don't want to be treated because they don't want to develop resistance. They want to wait. So the idea that there is another type of therapy that you could now cycle, that you could use with a course of IV antibiotics or with a course of oral floraquinolones might, in fact, take a bit of the selective pressure off.

CHAIRMAN CRAIG: Dr. Reller, you're one of our consultants, and I guess the question I would ask you is about the resistance. Is that a bothersome issue for you?

DR. RELLER: I look at this in a little

bit different way. Dr. Prince has emphasized this is the archetypical chronic obstructive. I mean, the end point is not eradication of the organism, and the numbers of organisms are astronomical. So that with every antibiotic that has been used with Pseudomonas aeruginosa, it is the one organism that virtually everything, if not everything, with exposure, resistance comes forth, but then it can recede.

One of the other interesting things about this high load is with some of the very nice studies done by Ogle & Vasil, the tenacity of Pseudomonas, but yet the plasticity having to do with phenotype, including antibiotic susceptibility, so that what we see here I look at more as evidence that there is a logical antimicrobial effect than being a problem. I mean, I see it as, you might say, a plus. Frankly, it is well within the range, if not much less than what one encounters with cycling, balancing, you know, other antimicrobials available.

Put simply, the data that I have seen are actually reassuring of -- I mean, they are a favorable point, not a negative point, having to do with the compound under consideration, and the way it is formulated and delivered.

CHAIRMAN CRAIG: My feeling also is the

type of resistance, with it being permeability, it really does tend to make the organism not as virulent, while betalactam resistances have not really shown that difference. So if I'm going to have to get one, I think I'd just as soon get one where it is going to make the organism a little bit more crippled than to get one where I'd still end up with a very virulent organism that would be able to continue to produce all of the enzymes and everything that would result in the damage.

DR. RELLER: And along with that, I mean, the bulk of these organisms are wiggling around the break point -- a break point that doesn't necessarily have anything to do with the situation in the lung. There are the permeability changes that are most influenced by divalent cations, which are very much different in the milieu of the obstructed mucoid-impacted bronchus versus the cation-adjusted Mueller-Hintonbroth.

And the most important thing in these patients -- and I think the most striking thing about what we've seen -- is that there clearly is improved pulmonary function, which is the measurable and reproducible end goal that has a lot of -- beyond lung function, functional benefits as well as for the

individual patient.

And the way these therapies are used, the patient serves as, in a way, their own control, because in a given patient, you know, the issue having to do with is six months enough, I would suspect that in an individual patient, if there were persistently no effect with inhaled tobramycin in a given patient that something else would be used.

And that doesn't mean that six months or three months or a year later that one couldn't come back to that same patient who has their own Pseudomonas aeruginosa that is going to be with them without the advent of some striking new therapy, fundamental new replacement therapy with them the rest of their life, that you could come back to this.

So I think what we're seeing here is more an index that there is an antimicrobial effect of inhaled tobramycin that cuts down on the number, does something to the organism, decreasing inflammatory things that -- insiders that they produce, and is in consonant with an effect rather than an indication of a safety problem.

CHAIRMAN CRAIG: Could I come back, Dr. Prince, and ask you what your feeling is about the data as far as its support for chronic use?

DR. PRINCE: There isn't any.

CHAIRMAN CRAIG: So that you would have difficulty basing a chronic use study on a six-month study?

DR. PRINCE: Well, no. I think -- when I say there isn't any, I don't --

CHAIRMAN CRAIG: There is no concern is what you're --

DR. PRINCE: No, I think there is always concern. But I think there isn't -- we really can't -- I would not expect a huge difference in what happens. If you doubled that period or extended it, you're going to see the isolates creep up as they have shown. But I don't think that there will be any major differences that we haven't seen, so I have no problem --

CHAIRMAN CRAIG: Okay.

DR. PRINCE: -- with chronic therapy.

CHAIRMAN CRAIG: Anybody else want -- go ahead, Nancy. Dr. Henry?

DR. HENRY: Well, I think that the drug, in some form, or I should say aerosolized antibiotics in some places are being used. So there is some concern with having children/adults get forms of antibiotics aerosolized that probably aren't good for

their lungs, given their preservatives.

And so I think there is some need to have a product out there that at least has been looked at for its safety as well as efficacy. And as others have said, the population of CF patients is probably the most diligent in terms of having adequate followup. And the patients often times are more informed than perhaps some of the young interns taking care of them.

(Laughter.)

You know, I guess my only thought is that I don't have any problem with the efficacy and safety, and I think there is a need to have the product approved.

But if it's approved as a twice-a-day, 28-day regimen, will that preclude really looking at it in a different way like once a day or maybe using it on a different duration? Are we locked in to that indication? And how readily could you come back and change anything?

DR. CHIKAMI: In fact, we don't have a specific question, but at the end we generally poll the committee if they have any recommendations about Phase IV studies. And, in fact, some of these issues that you've talked about -- different dosing regimen,

different length of therapy -- if you feel those are important, that those studies would generate important information on how to optimize use of the drug, in fact, you can make those recommendations.

CHAIRMAN CRAIG: Yes?

MS. ALTAIE: Sousan Altaie with the FDA.

Dr. Alexander had gone through an extensive analysis to demonstrate that there was a difference between 002 versus 003 in the effects we are all observing, and he could not pinpoint why the difference was there.

I was wondering if the sponsor itself has speculated why the differences are among the two studies.

CHAIRMAN CRAIG: I guess -- at least my understanding, there was not a difference in the primary end point, as far as FEV1. I mean, the percent improvement was a little less, but where the primary difference was was in the secondary end points in terms of hospitalization, IV antibiotic use, things like that.

DR. ALEXANDER: That's correct. I mean, there was an effect that was still there. It was lower overall in the protocol 003 than it was in 002 for the FEV.

CHAIRMAN CRAIG: Any response by sponsors? Any explanation that they might have for the differences between the two studies in secondary end points?

DR. PITLICK: We, in fact, looked very closely for reasons for the difference, and I'll let Dr. Montgomery talk about the results.

DR. MONTGOMERY: Since we're concerned about treatment effects, the differences between tobramycin and placebo at six months, the differences in the treatment effects between the two studies for FEV1 and FVC, the two primary end points, were very, very similar. The difference, though, was that there was a decline in the lung function in the 003 study in the placebo group which was not seen in the 002 study, suggesting that maybe there are some more intracurrent illnesses running in those centers that had that.

The explanations for differences in hospitalization and the IV antibiotic use, although we had those being a secondary end point, really are not clear to us. The IV antibiotic use is probably more reflective of what is really going on, because sometimes hospitalization, particularly in younger kids, is necessary because you can't have outpatient IV antibiotics.

So we thought the IV antibiotic use was more representative of the marker for exacerbation. And in both studies we saw very similar trends, albeit stronger in the 002 study.

Thank you.

CHAIRMAN CRAIG: Okay. Thank you.

Okay. I think -- I don't see anybody -- any more discussion.

Let's go ahead and take a vote on the first question, 1A. Do the safety and efficacy data presented support the approval of TOBI for the management of cystic fibrosis patients infected with Pseudomonas aeruginosa?

All those in favor of that motion, raise your hands. I see it as being unanimous.

So that leaves number B. We don't have to do that, and we can move on to question number 2. From the data provided in the subset analyses, are there specific groups for whom you would or would not recommend use of the TOBI?

And, again, if I go back and remember from the subset analysis that was presented by the FDA, the primary group in which there was not a difference in the FEV1 was primarily those that started -- or that's just in hospitalizations. Was there any subgroup in

which there was not an improvement in the primary indicator?

DR. ALEXANDER: In the primary indicator, no. In terms of the FEV, that was data that was shown by the sponsor before, and what we saw was in terms of statistical significance, for the youngest age group in whom the secondary end point seemed to improve more, there was a little bit less than effect but that were still statistically significant across the board.

CHAIRMAN CRAIG: Across the board. So nothing that really came out markedly in the subgroup analysis.

DR. ALEXANDER: Right. Unfortunately, I mean, we are talking about --

CHAIRMAN CRAIG: Numbers.

DR. ALEXANDER: -- much smaller numbers --

CHAIRMAN CRAIG: Yes. Yes.

DR. ALEXANDER: -- in terms of subset, so we only had the ability to look at trends.

CHAIRMAN CRAIG: Okay. Any comments or anything from any of the members or consultants? Any concerns about any subgroups?

Dr. Henry?

DR. HENRY: The study did not include Burkholderia cepacia patients. So does that mean that

there would be a contraindication to use that in that subset of patients who have Burkholderia?

DR. ALEXANDER: Those sorts of issues can be handled in product labeling.

DR. HENRY: Okay.

CHAIRMAN CRAIG: Okay. Seeing none, let's go on and -- we're on a roll.

From the data provided in the subset analyses, are there specific groups for whom you would or would not recommend use of TOBI? So I guess we're taking out the "would not." Are there subgroups you would recommend use?

Anybody recommending use, raise their hand. So we're going to not use it in certain ones. All those that think it should be available for all of the various subgroups, raise your hand. So that's, again, unanimous.

Okay. Given the safety information regarding changes in MIC for Pseudomonas aeruginosa, what additional recommendations would you make?

I can tell -- I'd do some population analyses in some of your future studies, so that you can identify the subpopulations to see what percentage they are among the total number of bacterial organisms, because that would be, I think, very useful

information to let us know whether it's just a small subset of organisms that are emerging with resistance or whether it is something that is affecting the large mass of organisms in these patients.

DR. PRINCE: Can I make a comment?

CHAIRMAN CRAIG: Yes.

DR. PRINCE: From Dr. Samen's study of multi-resistant organisms, just as Dr. Azimi mentioned, many centers that have automated testing can't accurately measure the MICs of many of the mucoid organisms. So it's critical that the sponsor be in charge of doing that, because you can't -- particularly with managed care, they take a swab and throw it in, and it's really not accurate.

CHAIRMAN CRAIG: It's very nice to do, because, I mean, aminoglycosides are exceedingly stable, so you can put them into ager and keep the ager around for long periods of time, because when we were doing this on patients on the wards, we could always keep a supply. And what we'd do is as soon as one collects a specimen is plate it out immediately onto the different ager.

And then, really, all you're doing is counting numbers, so you're trying to find out what percentage of the total population has high resistance

as compared to those organisms that may have lower MICs. So it's not really doing a specific MIC. It's just plating it in on ager-containing plates which the sponsor, I'm sure, could prepare and provide so that it would be uniform at all of the sites.

CHAIRMAN CRAIG: Any other -- Dr. Danner?

DR. DANNER: I guess the thing I'm wondering is whether we really know the mechanism by which the efficacy is occurring, because with the slides that were shown, the organism -- the effect on counts of organism is greatest at the beginning; it decreases over time. As the studies extended out for longer periods of time, the effect on bacterial counts per se may, in fact, be even less or nonexistent over time.

But you still potentially, I guess, could see the efficacy, because that didn't seem to change over time, at least during the six-month study. And I guess I'm thinking of Dr. Craig's comment about how maybe somehow by shifting the population of the organism that these organisms that are regrowing are somehow crippled and less likely to be able to cause disease, cause continuing lung injury.

And so I guess my recommendation would be to -- as I'm sure you're doing, to look at the

mechanism by which -- or alternative mechanisms by which this might be working, aside from just decreasing bacterial counts.

Is this new population of organisms that is coming out under the tobramycin pressure less able to make certain proteases or exotoxins associated with the organism? Is it somehow, in fact, less able to exist or cause disease in the environment of the lung in these patients? And not -- you know, it's not just a bacterial count phenomenon. It has something to do with the population of the organism.

CHAIRMAN CRAIG: Any other suggestions, comments, by anyone?

Dr. Reller?

DR. RELLER: It was mentioned that looking at the genotype of these organisms had been done. With some of the techniques that have been looked at, at the genetic sameness, but the phenotypic variation, I mean, it is conceivable that you have more resistant organisms after exposure, but organisms that are producing less bad things that insight the pathophysiologic changes that ultimately result in a decreased FEV1.

On these patients, do you have data on the sameness of their organism over time? That is, the

fundamental genetic sameness of their organism, regardless of the phenotypic variability, which has been demonstrated to be so great.

DR. MONTGOMERY: Yes.

DR. RELLER: They are the same -- basically, people carry their same organism.

DR. MONTGOMERY: Right.

DR. RELLER: And I think that's a very important concept, because, you know, these MICs can wiggle all over the place. But what those organisms are doing to that interface between the neutrophils and the patients' airways and how much air gets in and out is the fundamental issue. And that's why I think that subset analysis is -- that keeping the primacy a function at the four -- I mean, I'd be very concerned if a subset said changes in -- you know, not the same improvement in function. But the function is the issue in these patients.

CHAIRMAN CRAIG: And getting back, again, to what I had recommended as far as the population analyses, there is two times I think that that can be helpful -- is right at the end of therapy and then again at the month farther down the line just before you start, because the ones done right at the time of therapy might also pick up phenotypical resistance,

the so-called adaptive resistance that occurs in aminoglycosides.

It's not stable and reverts back. And often times that can occur very quickly, within one or two passages in drug-free media. That's gone, and then you're only left with those organisms that have a more stable permeability defect. So by looking at them right after therapy, and then again later on after they've had a time off, you'll get an idea of what is stable and what kind of adaptive resistance might occur actually when the drug is being administered.

Any other comments or suggestions?

Okay. Let's move on to number 4. Given the safety information regarding ototoxicity, what additional recommendations would you make?

Guess I can start and say I would, at least in a subset, or at least in a number of patients it would be sufficient to try and find it. I'd do some high frequency audiometry.

Studies have been done with -- you have to be careful. You need to try and do those in patients that aren't getting IV tobramycin, because there are studies published in the literature, probably in an older age group than this, but using very high

frequency audiometry they've seen a frequency of lesions as high as 40 percent in patients that have received one course of aminoglycoside.

So I would try and do it in those kind of patients that are not getting IV tobramycin, so that you might thereby have a chance to see if there is anything that is being produced by TOBI in terms of very high frequency defects that would be important for its use in the future.

Dr. Melish?

DR. MELISH: And I would focus on tinnitus evaluation, more about when it occurs, its character, what relationship it has to other events. I think it's -- these people will get enormous lifetime doses of aminoglycosides parenterally, which may be the most important determining factor as to whether they get otologic toxicity. But whether this is significantly additive over two years, 10 years, I think is going to be important.

CHAIRMAN CRAIG: Yes, Dr. Henry?

DR. HENRY: Well, I agree with Mary that to assess the tinnitus issue, especially in the younger age group -- the age six to 10 or six to 12 -- probably a bit harder to subjectively get at that -- an answer to that question than it would be with an

older child or an adult. That maybe those children need more frequent audiometric testing, and certainly at the higher frequencies.

You know, I think some CF patients would say they would take a little bit of deafness and hearing aids, and rather, you know, be alive to talk about it than to be deprived of something that could help them.

But the younger age population -- I think there is an obligation to make certain that we're not doing something to them at this age that would be a lifetime disability.

CHAIRMAN CRAIG: Any other comments, suggestions, or anything from any of the members? Did you get your questions answered, or is there anything else you'd like us specifically to ask?

DR. CHIKAMI: Let me just -- as I mentioned earlier, we usually ask for general recommendations on Phase IV. And you've certainly made a lot of recommendations related to our specific questions in regard to the MICs and the safety issue of ototoxicity. But let me just ask the committee if they have any other -- as they have heard the data presentation and the discussions, if they have any other recommendations for Phase IV studies.

CHAIRMAN CRAIG: Yes, Dr. Henry?

DR. HENRY: I would just be curious to know if it were -- if there is some way of looking at what the concentration of tobramycin would be in the sinuses. Obviously, if the sinuses are heavily colonized, and it drains down into the lower respiratory tract, is there some way of looking at levels of TOBI in the sinuses.

CHAIRMAN CRAIG: Already done.

DR. PITLICK: No, unfortunately. The system of administration is a handheld nebulizer, which is held in the mouth. And so we don't have -- most of the tobramycin is inhaled into the lungs rather than sinuses, but that's something we could consider.

DR. HENRY: I mean, the reason I bring that up -- although Pulmozyme is not really to be nebulized, a lot of the younger children are nebulizing it, and, therefore, are getting some up into the nasal passage and into the sinuses. And although it would probably change distribution -- I mean, I guess I don't know what three micrometer size particles do, how easily they get into the sinuses, if you use a conventional nebulizer, to look at what it might do in the sinuses.

DR. PITLICK: Well, it's certainly something we've talked about.

CHAIRMAN CRAIG: Dr. Reller?

DR. RELLER: One of the important things about having this drug available -- it provides something against which to compare other options, including, I think, Dr. Henry's question earlier. With persistent effect that is apparent between months -- that is, 28 days on and 28 off -- you know, it raises the question straightaway whether or not once a day would be sufficient in combination with the recombinant DNase that is used. So that that is one issue. If twice a day works, would once a day work also?

Plus, of course, other agents that -- where resistance, and particularly in a cycling program, for which resistance to Pseudomonas aeruginosa is either difficult to achieve or nonexistent, like polymyxin -- the polymyxins.

CHAIRMAN CRAIG: And the current plans are to continue the study for --

DR. PITLICK: We have continuing follow-on studies that are ongoing, which will give us an additional two years of experience.

CHAIRMAN CRAIG: Two years.

DR. PITLICK: But I'd also like to inject, as they say, a word from the sponsor here. We intend this to be a long and hopefully productive relationship with the Division of Anti-Infective Drugs. We have several other drugs that we are considering in the pipeline, some of which have different mechanisms of action against Pseudomonas, but also against B. cepacia and other organisms.

And so, I mean, our ultimate goal is to develop a portfolio of antibiotics which are suitable for the treatment of people with CF, so that, indeed, you can cycle.

We thought we'd try one at a time rather than doing them all at once, though.

(Laughter.)

CHAIRMAN CRAIG: Is that what you wanted to hear, then?

DR. CHIKAMI: Yes, I think so.

CHAIRMAN CRAIG: Okay. Well, I'd like to thank all of our speakers and the sponsor for staying in time and for presenting everything quite clearly to us.

I'd also like to thank all of the members, especially those that were here for all three days.

Thank you all, and the meeting is

adjourned.

(Whereupon, at 1:02 p.m., the meeting was adjourned.)